Newer Pathways of Carbohydrate Metabolism

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Despite the intensive efforts of biochemists and physiologists in the sixty years since Mering and Minkowski's discovery of the relationship between the pancreas and diabetes, we are still unable to say with any degree of assurance that we understand the defects in sugar metabolism underlying this disease entity. The hope held by biochemists for many years, and thought to have been realized several years ago,[1] that the biochemical lesion in diabetes would be found in a single chemical reaction somewhere along the pathway of glucose metabolism, has not materialized. It appears now that before such a Utopian condition is reached, we shall have to dig more deeply and thoroughly into the complex and devious metabolic routes followed by sugars in their interconversions and in their interactions with other foodstuffs and cell components.

It is in this area, however, that we can strike a more optimistic note. Our knowledge of the pathways of metabolism has broadened so greatly in recent years that in retrospect it seems that we must have been incredibly naïve a few years ago to have expected a clear-cut biochemical answer to the riddle of diabetes on the basis of knowledge available at that time.

I propose to explore with you our present conceptions of the chemical paths of glucose catabolism, and to dwell particularly on what I regard as one of the most exciting of the recent developments in carbohydrate metabolism—a new pathway of glucose dissimilation. I should like to map out those chemical pathways of carbohydrate metabolism which, on the basis of our present knowledge, are of importance in the metabolism of glucose in animal cells.

OUTLINE OF GLUCOSE METABOLISM

Figure 1 shows the over-all outline of glucose metabolism in cells of the higher animals. The first step is an activation by combination with phosphate, following which the hexose phosphate is split to a triose, then converted to pyruvic acid, and ultimately to acetic acid. The molecules of acetic acid mingle with identical acetic acid molecules coming from fatty acids and other substances and are converted to carbon dioxide by means of the so-called citric acid cycle. In this process acetic acid, in the form of an ester of coenzyme A, condenses with a molecule of oxalacetic acid to yield citric acid. This is then successively converted to isocitric, oxalsuccinic, alpha-ketoglutaric, succinic, malic, and oxalacetic acids. In a single revolution of the cycle one acetic acid molecule is completely oxidized to carbon dioxide and regenerates one molecule of oxalacetic acid to carry on the cycle. The regeneration of oxalacetic acid allows the cycle to continue indefinitely, with only trace or catalytic amounts of citric acid cycle components actually present in the cell at any time.

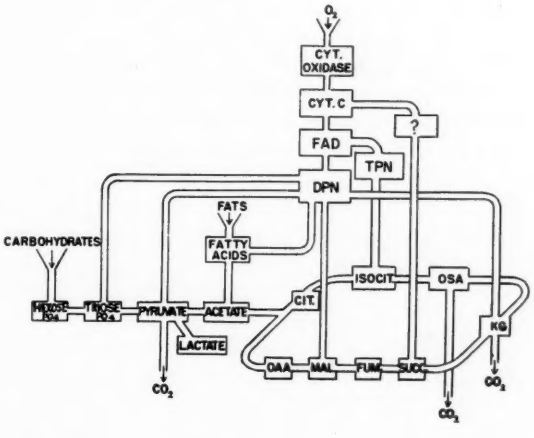

FIG. 1

In the course of the oxidation of a molecule of glucose by these means, twenty-four electrons are lost—twelve for each triose. These are given up at six oxidation steps; namely, triosephosphate, pyruvic acid, isocitric acid, alpha-ketoglutaric acid, succinic acid, and malic acid. These electrons ultimately combine with oxygen to yield water, but before doing so they pass through a series of electron transport agents, which like a bucket brigade, take a pair of electrons from one donor and hand them on to an acceptor, until they ultimately reach

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oxygen. These electron-transferring enzymes, arranged vertically in figure 1, have as coenzymes diphosphopyridine nucleotide (DPN), triphosphopyridine nucleotide (TPN), flavin adenine nucleotide (FAD), and the cytochrome system, including cytochrome c and other cytochromes whose precise function or position in this process is still uncertain. Components of this electron transport system are the well-known vitamins, nicotinamide and riboflavin. Carbon dioxide, which is the ultimate product of the oxidation of carbohydrate, is given off at three places in this process; the conversion of pyruvic to acetic acid, that of oxalosuccinic to alpha-ketoglutaric acid, and that of alpha-ketoglutaric to succinic acid.

As shown, the cycle appears to have only an oxidative function; however, it serves a more important service in the cell as a means of communication between the various foodstuffs and the cell components. For example, the cycle can supply carbon for various amino acids. Alanine can be formed from pyruvic acid, and thence to such other amino acids as serine, glycine, and cysteine. From glutamic acid there are pathways to other amino acids such as proline, hydroxyproline, ornithine and arginine. We can visualize the citric acid cycle as a means of communication between a major foodstuff such as carbohydrate on the one hand and almost any conceivable cell component on the other. All or most of these processes are reversible and thus provide pathways not only for the formation but also for the utilization of the amino acids and other cell components for energy production, or even for the production of sugar.

From the diagram, it is evident that acetic acid is a key substance, a focal point for the merging of the metabolism of both fats and sugar. The actual intermediate is not acetic acid as such but an ester of acetic acid with a new sulfur-containing coenzyme—coenzyme A. The mechanism by which pyruvic acid can be converted to acetyl coenzyme A has been greatly clarified in the past few years. This has emerged as an extremely complicated process, involving no less than five separate cofactors—thiamine pyrophosphate, magnesium, lipoic acid, coenzyme A, and diphosphopyridine nucleotide.[2]

The first step is the decarboxylation of pyruvic acid. This requires diphosphothiamine (DPT) and magnesium, and the products are carbon dioxide and a complex of acetaldehyde and diphosphothiamine. In certain organisms this complex may be oxidized directly to acetic acid, or converted to condensation products such as acetolactic acid or acetoin. In higher animals and in certain other organisms the diphosphothiamine group is exchanged for another new cofactor discovered only in recent years, lipoic acid. This is a new sulfur-containing coenzyme whose structure and function have been cleared up only very recently. This complex of acetaldehyde and lipoic acid then undergoes an intramolecular rearrangement of its electrons, resulting in an oxidation of the acetaldehyde to acetic acid and a reduction of lipoic acid, to yield an acetyl ester of reduced lipoic acid. The acetyl moiety is again transferred—from the reduced form of lipoic acid to coenzyme A yielding acetyl coenzyme A and free reduced lipoic acid. The lipoic acid then becomes oxidized via diphosphopyridine nucleotide back to the oxidized form and is now ready to accept and combine with another acetaldehyde molecule.

Acetyl coenzyme A thus formed has a choice of several pathways. By combining with oxalacetic acid it can be oxidized to carbon dioxide through the citric acid cycle, or it can undergo other types of reaction, such as fatty acid or cholesterol synthesis, or conversion to acetoacetic acid.

The evident complexity of the ostensibly simple reaction, the oxidative decarboxylation of pyruvic acid to form acetyl coenzyme A and carbon dioxide, which has emerged from a thorough study of just one step of the great many involved in sugar metabolism, indicates how superficial is our knowledge of cellular biochemistry.

PATHWAYS OF GLUCOSE CATABOLISM

I shall now take up a still earlier stage; namely, those reactions which give rise to pyruvic acid. Until a few years ago it was generally believed that the main, if not sole route of glucose catabolism was that developed in the previous generation by Embden and Meyerhof. Perhaps the most exciting of recent developments in carbohydrate metabolism is the realization that another pathway of glucose breakdown may play an important role.[3-5] The old and new pathways are shown in figure 2. In the Embden-Meyerhof pathway, on the right, glucose-6-phosphate is converted successively to fructose-6-phosphate, fructose 1, 6-diphosphate, and triose phosphate, ultimately to yield pyruvic acid. In this process each glucose molecule yields two trioses and two pyruvates. The new process has been called the direct oxidative process or the oxidative shunt, but perhaps a better name would be the pentose pathway. Glucose-6-phosphate is oxidized directly to 6-phosphogluconic acid. This is oxidized further, probably to 6-phospho-3-ketogluconic acid, and this is decarboxylated to yield carbon dioxide and a ketopentose, ribulose-5-phosphate. Ribulose-5-phosphate is split to a triose phosphate, which ultimately yields pyruvic acid and a "diose." This term is quoted because

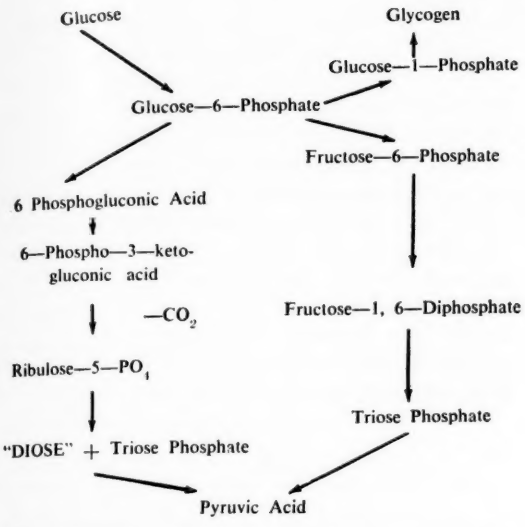


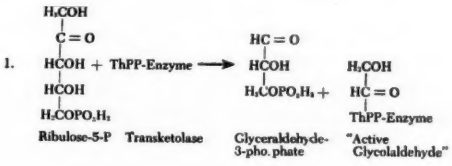
FIG. 2. Embden-Meyerhof and direct oxidative mechanisms of glucose catabolism.

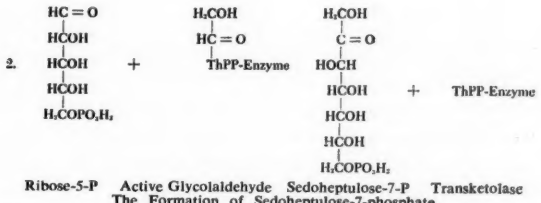
the substance has not yet been isolated and identified. It is presumably glycolaldehyde in the form of an enzyme complex.

The formation of the "diose" from ribulose is actually not as simple as pictured. As shown in equation 1 it appears apparently only in the presence of an acceptor and through the agency of the recently discovered transketolase. It is interesting that this enzyme has a coenzyme diphosphothiamine (or thiamine pyrophosphate shown here as ThPP, the same coenzyme involved in decarboxylation of pyruvic acid. The products are a triose and a "diose"-enzyme complex, the so-called active glycolaldehyde. This as yet elusive substance can be transferred to certain acceptor molecules. One such transfer is shown in equation 2.

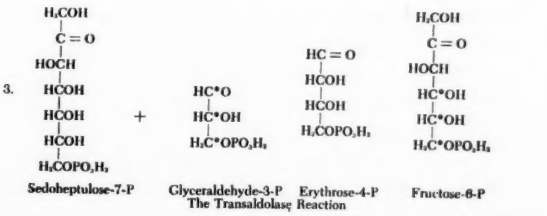
In the presence of an acceptor such as ribose-5-phosphate, which itself can be formed from ribulose phosphate through a specific isomerase, the "diose" group is transferred to yield a 7-carbon sugar phosphate, sedoheptulose-7-phosphate, and the free enzyme, which is now available for splitting another ribulose molecule. This 7-carbon sugar until a few years ago was a rare laboratory curiosity, found only in plants of the sedum family. It is now known to be a widespread intermediate of great importance, capable of being formed and utilized by almost every form of life through the series of reactions now being discussed.

In another similar transfer, shown in equation 3, the transaldolase reaction, a 3-carbon unit representing the first three carbons of the 7-carbon sugar, is transferred to another molecule of triose phosphate to give fructose-6-phosphate. This can be converted to glucose-6-phosphate to re-enter this direct oxidative process, or it may be converted to fructose-1,6-diphosphate, to enter the Embden-Meyerhof process. The other product of this reaction is an as yet incompletely identified tetrose, here designated as erythrose-4-phosphate. Ultimate disposition of this tetrose is not certain. One reaction it can undergo is shown in equation 4. This involves a transfer of a diose molecule from the first two carbons of ribulose phosphate to yield fructose-6-phosphate plus triose-3-phosphate.

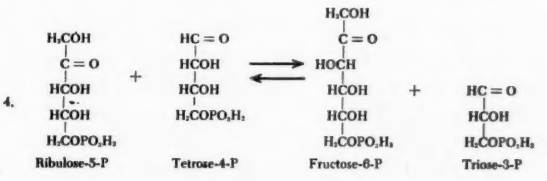




The Formation of Sedoheptulose-7-phosphate in the Transketolase Reaction.



The Transaldolase Reaction



The sum of all of these reactions is shown in figure 3. Three glucose molecules are phosphorylated by means of adenosine triphosphate (ATP), and there are obtained three molecules of carbon dioxide representing the oxidation of half a molecule of glucose. The other half appears as triose phosphate, which can undergo successive conversions to pyruvic acid and acetate. Simultaneously, two molecules of fructose phosphate are regenerated. Thus we see that the occurrence of all of these reactions constitutes a new oxidative cycle in which many intermediates participate, and which ultimately results in the oxidation of glucose.

OXIDATIVE CYCLE BASED ON TRANSKETOLASE AND TRANSALDOLASE REACTIONS

1. 3 Glucose + 3 ATP ⟶ 3 Glucose-6-Phosphate
2. 3 Glucose-6-Phosphate ⟶ 3 6-Phosphogluconic Acid
3. 3 6-Phosphogluconic Acid ⟶ 3 Ribulose-5-Phosphate + 3 CO_2
4. Ribulose-5-Phosphate ⟶ Ribose-5-Phosphate
5. Ribulose-5-Phosphate + Ribose-5-Phosphate ⟶ Sedoheptulose-7-Phosphate + Triose-3-Phosphate
6. Sedoheptulose-7-Phosphate + Triose-3-Phosphate ⟶ Fructose-6-Phosphate + Tetrose-4-Phosphate
7. Tetrose-4-Phosphate + Ribulose-5-Phosphate ⟶ Fructose-6-Phosphate + Triose-3-Phosphate

SUM: 3 Glucose + 3 ATP ⟶ 3 CO_2 + Triose-3-Phosphate + 2 Fructose-6-Phosphate

FIG. 3

We still do not know how important this series of reactions may be or how extensively it occurs in animal tissues generally. Glock and McLean[6] have found that most animal tissues contain glucose-6-phosphate dehydrogenase, and also enzymes for the utilization of 6-phosphogluconic acid and ribose-5-phosphate. The only tissue in which these enzymes are low is muscle. On the reasonable assumption that the presence of enzymes denotes occurrence of a process, it seems probable that this new pathway of glucose metabolism may operate generally in animal tissues. However, there is considerable interest in establishing the extent to which this process *does* operate in animal tissues, and to what extent dietary, hormonal, and other factors might influence its participation in sugar catabolism. Isotopic tracer procedures, using labeled glucose molecules, have been applied to this problem, but much of these data are in a controversial state because of difficulties of interpreting results.[7-9]

In our own laboratory, my associates and I have developed a direct and fairly reliable procedure for determining the relative proportions of the pentose and Embden-Meyerhof processes, and have applied this to a variety of cell types.[10] Time will not permit a description of the principle of this procedure, which also involves isotope tracers. Thus far we have done little more than survey representative cells. Some results obtained are shown in table 1. In liver slices and homogenates the direct oxidative process occurs to a variable degree. In rat liver the Embden-Meyerhof process is preponderant, but in mouse liver about 50 per cent or more of the glucose appears to be metabolized via the oxidative process. On the other hand, kidney, brain, and heart muscle appear to utilize only the Embden-Meyerhof process. One of our motives in carrying out this study was to determine the extent of occurrence of this process in neoplastic tissues. In these tissues a wide range of patterns was observed, ranging from complete Embden-Meyerhof to predominance of the pentose path.

TABLE 1
PATHWAYS OF OXIDATION IN TISSUES

Tissue	Embden-Meyerhof pathway Per cent	Direct oxidative pathway Per cent
Liver, rat and mouse	12-46	54-88
Kidney, rat	100	0
Heart, rat	100	0
Brain, rat	100	0
Mammary carcinoma, mouse	82	18
Rhabdomyosarcoma, mouse	91	9
Ascites TA_3 carcinoma, mouse	32	68
Hepatoma 98/15, mouse	100	0
Sarcoma 37, mouse	57	43

If these studies in vitro reflect occurrences in the intact cell, and if we can assume that the oxidative pattern in heart muscle is similar to that occurring in skeletal muscle, it would seem that the oxidative process does not play an important quantitative role in the over-all metabolism of glucose in the whole animal. Thus far the liver seems to be the only tissue utilizing this process, and this tissue probably represents only a relatively small proportion of the active glucose-metabolizing tissue of an animal. However, much more work will have to be carried out before any generalizations can be made with regard to the significance of this new pathway. The extension of these studies to other specific animal tissues and the study of possible factors which may regulate or control the relative participation of each of these pathways are topics of current interest.

SIGNIFICANCE OF DIRECT OXIDATIVE PATHWAY

Any special significance of the direct oxidative pathway is as yet uncertain, but several interesting possibilities are evident. Of course it probably serves an extremely important function in providing a mechanism for formation of ribose, a constituent of a host of cell components,

including nucleic acids. We have already seen that the net result of the efficient operation of the direct oxidative process results in a cycle of oxidation of hexose. The possibility exists that this cycle may operate in certain tissues as a supplement to or a replacement for the citric acid cycle. Much evidence already available indicates that this process may be of greater importance in the metabolism of plants and micro-organisms than in animals. For example, it is now clear that the process of photosynthesis, whereby green plants synthesize carbohydrate from carbon dioxide and light energy, involves components of the oxidative shunt.[11] The 7-carbon sugar, sedoheptulose, also appears now to be a carbon source of the aromatic amino acids, phenylalanine, tyrosin, and tryptophan.[12]

CONCLUSIONS

Thus far these new findings have complicated rather than clarified the diabetes picture. Our view of the intermediary metabolism of carbohydrate, which formerly extended to a few hexoses and trioses, now must be broadened to include dioses, tetroses, pentoses, and heptoses. We are confronted with the disturbing recognition that many more components, many more enzymes, many more factors are involved in the mosaic of metabolism than was considered possible just a few years ago. These are facts that confront us in our attempt to unravel the forces which control and direct the metabolism of carbohydrate.

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SUMMARIO IN INTERLINGUA

Nove Vias del Processos del Metabolismo de Hydratos de Carbon

Usque pauc annos retro, le conception general esseva que le processo del catabolismo de glucosa in le cellulas sequeva plus o minus exclusivemente le via describite per Embden e Meyerhof con le sequente passos: glucosa → glucosa-6-phosphato → fructosa-6-phosphato → fructosa-1, 6-diphosphato → 2 triosa-phosphato → 2 acido pyruvic. Il deveni de plus in plus obvie que un altere via es possibilemente disponibile al metabolismo de glucosa. Iste via diverge ab illo de Embden e Meyerhof in tanto que illo involve le oxydation de glucosa-6-phosphato in acido 6-phosphogluconic e hinc in ribulosa-5-phosphato. In le presentia de aldosas acceptores, ribulosa-5-phosphato es findite in triosa e glycolaldehydo active. Iste glycolaldehydo active se adde a un acceptor e forma un nove phosphato de sucro. Con ribosa-5-phosphato, iste reaction transcetolasic—como illo ha essite appellate—resulta in sedoheptulosa-7-phosphato. Alora sedoheptulosa-7-phosphato transfere—in le presentia de triosa-phosphato e le enzyma transaldolase—un portion de triosa al triosa-phosphato lo que resulta in tetrosa-phosphato e fructosa-6-phosphato. Assi le processo sequente iste nove via es un processo cyclic de oxydation e regeneration de hexosa. Le signification de iste processo in cellulas animal remane incerte. Provas de su occurrentia a un appreciabile grado ha essite obtenite solmente in le caso del hepate, del glandulas mammari, e de certe tumores, sed le enzymas involvite in illo se trova extensemente in le cellulas animal.

Remarks on Protein Metabolism

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Protein metabolism interests physicians because it is intimately related to the nature and behavior of living tissue. As the substance of life itself, little is known of protein, but a few of the factors concerned in the maintenance of normal tissues are listed in table 1.

TABLE 1
Selected Features of Protein Metabolism

Principal factors in the maintenance of normal tissues include:

1. Protein intake—quality and quantity.
2. Caloric intake—much but not all can be from fat.
3. Some utilization of carbohydrate is essential.
4. "Wear and tear" replacement, or endogenous and exogenous metabolism, vs. exchanges within a protein "pool."
5. Anabolism and catabolism; terms which represent the net or over-all balances of the building up and breaking down of protein.
6. Behavior of individual tissues (organs, species, etc.) within any over-all balance.
7. Hormonal influences on protein metabolism.

The first three headings serve to recall familiar sections of the textbook chapters.[1-3] It is well established that the maintenance of normal tissue depends on an adequate intake of protein in the diet. The word "adequate" means that the quality of the protein must be satisfactory; that is, the protein must provide the ten essential amino acids which man cannot synthesize. The amount of protein ingested must also be satisfactory, and this requirement varies in growth, age, or disease. Less protein is needed and the body protein is better conserved when there is an ample caloric intake. This does not mean overeating to the point of obesity. It does mean that protein will be called on for only a minimum of oxidation for mere calories. It means that exchanges within the protein pool can take place with the greatest efficiency. It also means that ample calories for protein synthesis are provided.

The statement that less protein is needed when the caloric intake is ample applies within the usual limits of dietary intake. However, when a large amount of carbohydrate and fat is eaten with minimal or deficient protein, fatty degeneration of the liver occurs. It seems proper to say that, in the presence of a large caloric intake, the dietary protein may have to be increased by an amount sufficient to protect the liver. In other words, there must be a suitable protein:calories ratio if liver damage is to be avoided.

Although most of the calories needed for the synthesis of protein can be provided from fat, it is clear that the utilization of some carbohydrate is absolutely essential. This is equally true during fasting, when protein is mobilized but the carbohydrate derived from it prevents indiscriminate catabolism. On the other hand, in pancreatic diabetes the excessive mobilization of fat and the greatest possible oxidation of ketones fail to protect the animal from an accelerated protein catabolism. The nitrogen excretion of the fasted depancreatized animal is twice that of the fasted normal animal.

One must go beyond insulin and carbohydrate to account for the negative nitrogen balance of fever, postoperative reactions, hyperthyroidism, and similar stresses. The loss of body protein in these circumstances can occur without glycosuria or diabetes. It therefore appears that the utilization of carbohydrate which is effective for normal fasting animals, or for the normal protein sparing action of carbohydrate, fails to protect the person whose total metabolism is accelerated by the stress of disease. The outline (table 1) does not include this relation of protein metabolism to the total oxygen consumption (of stress).

The old concept of "wear and tear" replacement of protein will not satisfy the modern chemist who studies the incorporation and exchange of isotopically labeled amino acids. From White's[2] summary of the modern studies three facts may be selected to indicate the meaning of the current concept of the "continuing metabolism" of nitrogen. (1) When nitrogen balance was maintained with nonsulfur-containing amino acids, the excretion of sulfur in the urine exceeded the basal or "endogenous" sulfur excretion. Whether body nitrogen was spared by protein or by nonsulfur-containing amino acids, the same amount of sulfur was contributed to the urine by tissue sources. (2) Active resynthesis of protein may occur even in the starved animal. (3) In a well-fed subject in nitrogen equilibrium, the "wear and tear" quota of nitrogen

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should be supplied by the diet and excess nitrogen should be excreted. Nevertheless, the protein sparing effect of carbohydrate occurs in such subjects. These and other observations have led to the present-day understanding of protein metabolism. This pictures the organism as a dynamic system, that is, an integration of continuing processes.

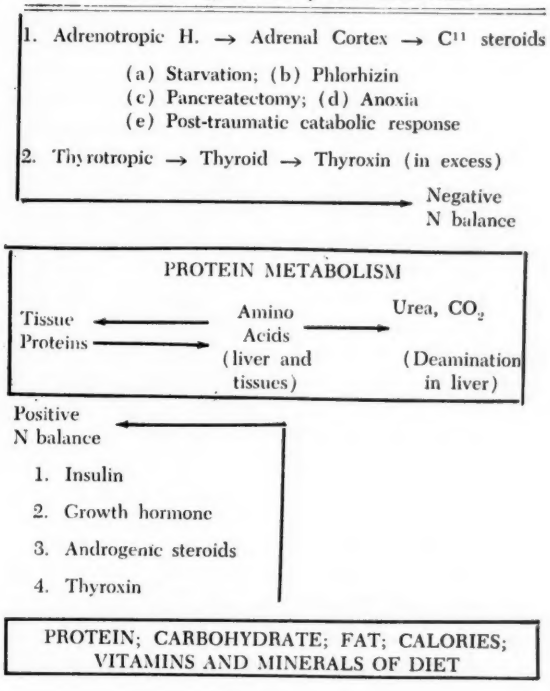
Although there is little or no store of protein in the body, apart from normal tissue, certain tissues, notably liver and lymphoid tissue, yield their substance most readily when the body needs protein or carbohydrate for such crises as starvation, stress, or healing. The response to such stimuli is mediated in part by the endocrine system, which appears to regulate the synthesis or breakdown of tissue protein as distinct from dietary protein. Hence, the amount of protein involved in response to a hormone may be small and may escape detection if one is examining the over-all nitrogen balance when the food intake is large. In other words, a small but important effect on the tissues may be masked by the larger turnover of dietary protein.

The terms "anabolism" and "catabolism" commonly refer to the net balance of the body as a whole. It is well recognized that within this over-all nitrogen balance, there may be many combinations of local tissue synthesis and breakdown. The study of the behavior of various tissues is just beginning.

Imposed on all these elements, or within this framework, there is a hormonal regulation of protein metabolism. This is outlined in table 2. Note that all endocrine regulation is pictured as acting on the basic structure of protein, carbohydrate, and fat available to the body. The central rectangle encloses the most elementary outline of protein metabolism. This contains the reversible reaction between amino acids and tissue proteins and the irreversible process of deamination by the liver. Above this diagram of protein metabolism, the principal catabolic stimuli and the hormones which facilitate a catabolic reaction of the body are listed. In this case the conventional negative balance is used to portray catabolism.

Below the diagram of protein metabolism are listed the anabolic hormones which favor or which tend to favor a positive nitrogen balance. Almost nothing is known of the anatomical site of action, or of the biochemical mechanism of any of the hormones which influence protein metabolism. We do not comprehend the complex synergism between those hormones which may work in a common direction. We do not understand the remarkable regulation between anabolism and catabolism. This means that it is all the more important for the physician

TABLE 2
Hormonal regulation of protein metabolism


1. Adrenotropic H. → Adrenal Cortex → C11 steroids
(a) Starvation; (b) Phlorhizin
(c) Pancreatectomy; (d) Anoxia
(e) Post-traumatic catabolic response
2. Thyrotropic → Thyroid → Thyroxin (in excess)
Negative N balance
PROTEIN METABOLISM
Tissue Proteins
Amino Acids (liver and tissues)
Urea, CO2
(Deamination in liver)
Positive N balance
1. Insulin
2. Growth hormone
3. Androgenic steroids
4. Thyroxin
PROTEIN; CARBOHYDRATE; FAT; CALORIES; VITAMINS AND MINERALS OF DIET

to select and keep in mind a few of those facts which may aid his comprehension of disease and his care of patients. Let us revert to the list of factors which influence the maintenance of normal tissues.

1. Most human dwarfism is due to genetic defects or to malnutrition. Malnutrition in turn may be due to a deficiency in the quality or quantity of protein; a total dietary deficiency due to economic circumstances or to gastrointestinal or other disease; one of the special forms of malnutrition due to vitamin deficiency; or one of the rare endocrine causes of malnutrition. Certainly no hormone will be of any help unless the diet and its utilization are adequate.

2. Ketonuria is one of the most useful indices of an actual or potential negative nitrogen balance. A glance at the list of stimuli (table 2) from starvation to the post-traumatic response will recall what this means. Ketonuria will reveal all forms of protein malnutrition, but its usefulness in many conditions is often neglected.

3. The catabolic reaction to disease or injury is greatest if the subject is originally well nourished. Whether it is chance or the wisdom of nature, the cachectic patient will react much less in terms of nitrogen

loss. The healthy person can tolerate fairly brief insults with an old-fashioned disregard of the incidental protein catabolism. On the contrary, in chronic disease accompanied by protein malnutrition, such as severe ulcerative colitis, one is often confronted with the dilemma of how much nutritional improvement can be secured before radical surgery or how much and how soon radical surgery can lead to improvement. Cortisone is labeled as a protein catabolic agent, but in selected patients its effect on appetite much more than offsets its catabolic tendency. Whether one is dealing with diet, drugs, or surgery, the net effect must always be estimated as well as possible.

4. In certain diseases such as hepatitis, cirrhosis of the liver, the nephrotic syndrome, sprue, and others, in which protein deficiency exists, there has been a tendency to prescribe excessive amounts of protein. In Cecil's text[4] high-protein diets (100 to 200 gm. daily) are recommended in hepatitis and after cholecystectomy. It would seem that an adequate amount should be given, and no more. Ideally, treatment should enable the diseased body to use protein, rather than flood it with protein it cannot use. Certainly no such forcing of protein should violate the principles of good nursing by turning the patient still more against his food. In relation to liver disease, Sherlock and co-workers[5] have described cerebral disturbances in eighteen patients, in whom the neurologic signs were precipitated or enhanced by giving ammonium chloride or methionine or by increasing dietary protein above 60 gm. daily. Their study was completed by reducing the nitrogenous content of the diet after which the mental symptoms abated.

In discussing the management of the nephrotic syndrome, Atchley[4] notes that current knowledge of albumin synthesis is too limited to warrant specific suggestions. He also notes that one can induce a positive nitrogen balance without altering the serum protein. This may be contrasted with the good response to a normal diet when the low level of serum proteins is due to malnutrition.

In all that I have said in this section, I agree with these authors[4] and with the summary of Co Tui[6] that a high protein intake is desirable when it can be successfully used for the replenishment of protein depletion and to accelerate convalescence. Physicians should, however, understand certain exceptions to the commonly accepted policy of large protein intake.

5. The growth-promoting effect of thyroxine in children with cretinism and the catabolic influence of hyperthyroidism show that an optimal level of oxygen consumption, or thyroid function, is needed for normal protein metabolism.

6. Recent studies have indicated that both the androgens[7] and growth hormone[8] require the presence of insulin to exert their anabolic effects.

7. This essential role of insulin in protein metabolism was perhaps first recognized by the occurrence of diabetic dwarfs. As diabetic dwarfism is unusual in the postinsulin era, the record of a recently observed patient is appended to this report. Here it is enough to note that the increased insulin needed for growth must be anticipated by the physician. By the use of depancreatized cats treated with varying amounts of insulin, we[8] have found that three to four times the maintenance dose of insulin was needed if growth hormone was to have its full effect. No wonder the child who received only a quarter of the amount of insulin which he needed at age fifteen, did not grow.

In conclusion, the physician who is thinking of the problems of protein metabolism will never forget the quality and quantity of the protein intake, the caloric intake, and the disease states which interfere with protein metabolism. He may find that ketonuria is a useful index of protein catabolism under certain circumstances, and that the post-traumatic catabolic response is less important than the underlying condition of the patient. He will not force protein in excessive amounts to the extent of interfering with good nursing. He will see that hormones are properly used to correct those rare disorders of protein metabolism in which hormones such as thyroxine or insulin may play a part.

CLINICAL ABSTRACT

An eight-year-old boy (B.T.) had been well until four weeks before his admission in December 1941. At that time his parents had noticed nocturia and excessive thirst. He was taken to a doctor, who tested his urine, diagnosed the condition as diabetes, and put him on a diet. This controlled the thirst and polyuria, but glycosuria persisted. Several days before his admission he had developed pharyngitis, fever, vomiting, and abdominal pain. He had had little food or fluid for three days before admission. In the hospital, the diagnosis was acute pharyngitis and diabetic acidosis with impending coma.

Course and Management. The acidosis was readily controlled and the blood sugar was normal by the third day. Instead of reducing insulin rapidly the dose was gradually lowered until the patient had a normal fasting and postprandial blood sugar without insulin six weeks later. He was discharged on a diet of protein 75 gm., fat 95 gm., and carbohydrate 180 gm. per day and no insulin on Feb. 14, 1942. His weight had increased from 65 to 77 pounds in this time.

As commonly happens in children, control by diet was unsatisfactory and the patient was readmitted in March 1942 for regulation. This time he was discharged free of glycosuria on the same diet and 10 units of protamine insulin daily.

The patient was again admitted on May 16, 1949, at the age of fifteen. At this time the chief complaint was failure to grow. His parents had noticed no growth since the age of eight, and his thirteen-year-old brother was three inches taller than he. In the seven years since his last admission he had been on the same diet (probably exceeded?) and 15 units of insulin. For the last two years the dose had been 20 units of protamine insulin.

On examination, the height was 4 feet, 8 inches and the weight 96 pounds. He had the general appearance of an eight- to ten-year-old child; his voice had changed; he was somewhat paunchy but was otherwise normally proportioned; he was intelligent. There was no axillary or pubic hair. There was mild otitis media. The genitalia were underdeveloped. X-ray examination showed the bone age to be about twelve years. Glycosuria and acetonuria were 4+. The temperature was normal. The otitis subsided promptly on treatment with penicillin. The diabetes was finally regulated with protamine-zinc insulin 40 units and regular insulin 30 units in the morning, 10 units in the evening, a total of 80 units daily. The diet was increased to P 100, F 90, C 250. In the last four days of this regimen the patient had fasting blood sugars of 100 and 102 and one blood sugar at 9 p.m. of 150 mg. per 100 cc. Quantitative glycosuria on May 19 was 22 gm. per day; on May 26 and 27 it was zero.

Final inquiry by telephone in October 1953 yielded the following information. The patient was then twenty years old. The height was 5 feet, 3 or 4 inches, that is, he had grown at least 6 inches since 1949. He had graduated from school and was working regularly.

Note that one-quarter of the insulin needed at age fifteen had resulted in diabetic dwarfism. The striking growth when enough insulin was used needs only the comment that this child was very well fed at all times as far as we could tell.

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SUMMARIO IN INTERLINGUA

Remarcas Super le Metabolismo Proteinic

Es revidite alicunes del factores que influe super le metabolismo proteinic. Es signalate le importantia del qualitate in ultra le quantitate del ingestion de proteina. Minus proteina es requirite quando le ingestion caloric es ample. Un grande portion ben que non le totalitate del requirimentos caloric pote esser fornite per grassias. Un certe utilisation de hydratos de carbon es indispensabile pro assecurar un correcte uso del proteinas. Isto es indicate per le negative balancia proteinic del patiente de diabete sever qui ancora oxyda grassia tanto ben como per le individuo non diabetic. Ben que il non ha un reserva de proteina in le senso stricte, le hepate e le texitos lymphoide age como un "reservoir texital." Iste texitos contribue plus que altere texitos in le fornimento de proteina. Le metabolismo proteinic se basa super un metabolismo de proteina, hydrato de carbon, e grassia, como etiam super le calorias, vitaminas, e minerales del dieta. Es superimponite a iste fundo nutritional un regulation endocrin del metabolismo proteinic del texitos (metabolismo proteinic endogene). Iste regulation per medio de hormones es delineate. Illo es illustrate per le reporto de un patiente con nanismo diabetic causate per inadequate dosages de insulina.

Normal Lipid Metabolism

Samuel Gurin, Ph.D., Philadelphia*

Very striking advances have been made recently in our understanding of lipid metabolism. Much of this has come about because biochemists have learned how to prepare cell-free preparations without producing too extensive destruction of intracellular enzyme systems. The tremendous advantages of this type of technic are obvious. Once a cell-free preparation is available, the various particulate fractions of the cell can be separately studied for enzymatic activity. If, in addition to this, it becomes possible to extract from these particles the water-soluble enzymes capable of performing a series of metabolic reactions, then the way is open for a final attack. Every energy of the chemist is devoted to obtaining aqueous solutions of such enzyme mixtures since this permits him to fractionate and separate individual enzymes. Once this has been achieved, it becomes possible to study single reactions of an otherwise complex series of metabolic reactions. With a single enzyme, the reaction product accumulates; in a mixture of enzymes, the reaction product is metabolized further and does not accumulate. It is obvious that studies with the whole animal or with a whole organ can provide answers concerning starting material and end-products. Almost never can such studies yield direct evidence of the nature of the intervening reactions.

It is a source of great satisfaction that both the oxidation of fatty acids as well as their synthesis have now been accomplished in aqueous particle-free enzyme solutions. Such studies have demonstrated conclusively that the initial oxidative attack upon fats involves the formation of activated fatty acids. Such activated acids have now been shown to be combined through their acid groups with coenzyme A (a pantothenic acid derivative containing a sulfhydryl group). The resulting activated product is a thiol ester (figure 1) which is now capable of undergoing the classical beta oxidation process. The important point to remember is that, although this involves the usual beta-hydroxy and beta-keto acids as intermediates, the coenzyme A group still remains firmly attached to the carboxyl or acid radical. When a two-carbon fragment is finally broken off, it is released not as acetic acid but as acetyl coenzyme A. The remaining fatty acid is now shorter by two carbons, but is still attached to a second coenzyme A molecule which was introduced when the acetyl coenzyme A fragment was split off. The process can now be repeated a number of times until the fatty acid coenzyme A complex has been completely broken down to acetyl coenzyme A. The major product of fatty acid oxidation in all cells is therefore acetyl coenzyme A. Incidentally the major product resulting from the decarboxylation of pyruvate (derived from carbohydrate) is also acetyl coenzyme A. This coenzyme A derivative of acetate is therefore the important metabolic intermediate common to both carbohydrate and lipid catabolism. The fate of this substance is accordingly of paramount importance for an understanding of the metabolism of fats, carbohydrates and, to some extent, protein.

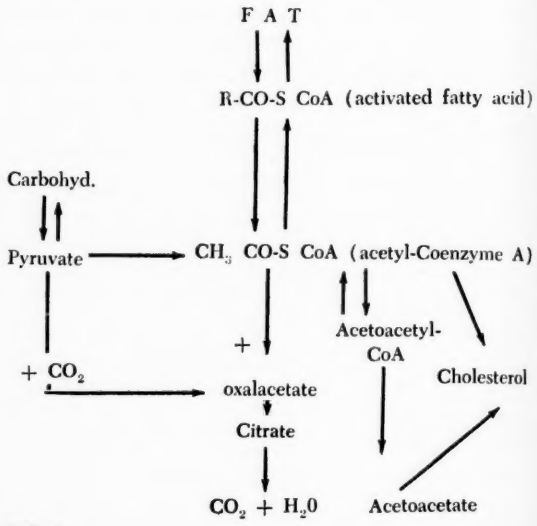

FIG. 1

Utilizing purified enzyme systems it has now been established that acetyl coenzyme A can act as follows:
1. It can condense with oxalacetate to form citrate.
2. It can condense with itself to form acetoacetyl co-

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enzyme A (ketone bodies). 3. It can condense with itself and with short-chain fatty acid coenzyme A derivatives to form long-chain fatty acids. 4. It is capable of condensing with acetoacetate to form the major building stones for cholesterol synthesis. 5. It is an important biological acetylating agent.

Reaction 1 clarifies the way in which fatty acids and carbohydrate are oxidized to carbon dioxide and water. Both give rise to acetyl coenzyme A which can promptly condense with oxalacetate to form citrate which is oxidized efficiently by way of the Krebs citric acid (tricarboxylic) cycle. Although this cycle regenerates oxalacetate which should therefore be required only in catalytic amounts, situations may arise where the available amount of this substance may be inadequate. If, for example, fat is mobilized and transported to the liver in abnormal quantities, and if excessive amounts of acetyl coenzyme A result from an accelerated breakdown of fatty acids in the liver, such conditions might prevail. If the amount of oxalacetate available then becomes insufficient, the excess of acetyl coenzyme A must be channeled into other pathways. Condensation of two molecules of acetyl coenzyme A will yield one molecule of acetoacetyl coenzyme A. This is a reversible reaction.

$$2\ CH_3\ CO\text{-}S\ CoA \rightleftharpoons CH_3\ CO\ CH_2\ CO\text{-}S\ CoA + CoA$$

$$CH_3\ CO\ CH_2\ CO\text{-}S\ CoA \longrightarrow CH_3\ CO\ CH_2\ COOH + CoA$$

and acetoacetyl coenzyme A is therefore capable of being readily oxidized by liver to carbon dioxide and water. In liver, however, the coenzyme A can also be readily removed from acetoacetyl coenzyme A yielding acetoacetate. Since liver is relatively incapable of reactivating acetoacetate (cannot make acetoacetyl coenzyme A from acetoacetate) we can understand why the ketone bodies are inert in liver. They must therefore be transported to extra-hepatic tissues where there are available enzyme systems capable of once again forming acetoacetyl coenzyme A from acetoacetate. One other point needs to be made. Although pyruvate readily gives rise to acetyl coenzyme A, it can also react with carbon dioxide to form oxalacetate or its equivalent, malate. Whether or not the diabetic state is associated with a relative lack of oxalacetate (since pyruvate is derived from glucose) is not clear. Whatever the reasons, it is clear that when carbohydrate utilization is impaired, overwhelming amounts of acetyl coenzyme A are produced in the liver. If oxalacetate becomes limiting, then ketone body formation must increase. Since such conditions are associated with increased quantities of acetoacetate and acetyl coenzyme A, it is not surprising that accelerated cholesterol synthesis may also frequently occur. It has previously been pointed out that these two substances are important precursors of cholesterol.

Another channel open to acetyl coenzyme A is the resynthesis of fatty acids. It is now clear that acetyl coenzyme units can condense to form long-chain fatty acids; the conversion of carbohydrate to fat involves therefore preliminary glycolysis of carbohydrate to pyruvate which is subsequently decarboxylated to acetyl coenzyme A. In vitro experiments with acetyl coenzyme A indicate that it can form all of the carbon atoms of fatty acids. Strangely enough, this synthesis of fat from acetyl coenzyme A appears to require the simultaneous participation of rapid glycolysis. Liver tissue from a previously fasted or alloxanized rat (or depancreatized cat) appears to be unable to synthesize fat from acetyl coenzyme A. In diabetes therefore, another channel for the utilization of acetyl coenzyme A is closed off, and this provides still more reason for the ketosis of diabetes.

It may well be asked why pyruvate is antiketogenic even though it is a ready source of acetyl coenzyme A. A ready answer could be made that pyruvate not only can yield acetyl coenzyme A but can also provide its own oxalacetate by fixation of carbon dioxide. This, at least, provides a reasonable explanation for the antiketogenic action of carbohydrate. It could also be argued, of course, that anything operating to reduce the amount of fat pouring into the liver would have a similar effect.

I mention these points to make it obvious that there are a few unsolved problems left. Even the most skeptical must now, I think, admit that studies with isolated enzyme systems have yielded significant results. The difficulties arise when the attempt is made to interpret such findings in the light of the known physiological behavior of the intact cell, tissues or whole animal. This is undoubtedly the most difficult task of all, but is one that the mammalian biochemist always must keep in mind.

SUMMARIO IN INTERLINGUA

Normal Metabolismo de Lipidos

Progresso in le comprension del metabolismo de lipidos ha essite effectuate per le utilisation de purificate systemas enzymic. Il ha essite possibile demonstrar que le major producto del oxydation de acidos grasse in omne cellulas es acetylcoenzyma A. Isto es etiam le major producto del discarboxylation de pyruvato (derivate de hydratos de carbon). Assi illo es le importante intermediario metabolic commun al catabolismo de e hydratos de carbon e lipidos. Su varie actiones metabolic es discutite.

Normal Metabolism
Panel Discussion

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Moderator

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Toronto

Francis D. W. Lukens, M.D.‡
Philadelphia

William C. Stadie, M.D.§
Philadelphia

Sidney Weinhouse, Ph.D.||
Philadelphia

MODERATOR GURIN: Normal metabolism means the metabolism of the normal intact animal. Chemists and physiologists have been attempting to get at the intimate mechanism of complicated reactions within the body cells; it is difficult to get these intimate facts in studying the whole animal. Then of course, the supreme job remains for the skillful physiologist and chemist to put all these facts together again and to try to get complete understanding of the whole business.

We haven't talked very much about the role of the hormones in these metabolic processes. It has been a very difficult business in trying to pin down how these endocrine mechanisms work. It seems to me that life is a whole bunch of reversible reactions and that this is a very convenient way of not having things happen in explosive fashion. Physiological metabolic events are a resultant of a number of factors: how much starting material or food or fuel goes into the system and what happens to the end products; the rate with which they are removed from the organism or from the cells in question. Whether or not hormones really play a part in this particular region I don't know. I am optimistic enough to feel that there is some chance that they do.

This is an area that this panel might well discuss. We haven't discussed, for example, such questions as the mobilization of fat, an area in which Dr. Best could tell us a great deal, and there are a number of other points that need to be brought up. I should like to call on Dr. Best first to talk about anything he pleases; anything that has occurred to him during this discussion.

DR. BEST: It was suggested by Dr. Gurin that I talk about carriage of fat—the mobilization of fat in the body. Our teaching has changed tremendously over the last years on this subject. I would teach now that almost all of the fat is absorbed into the lymphatics, that you can cannulate the abdominal lymph vessels and collect nearly 100 per cent of the fat which disappears from the intestinal tract and that the pathway to the blood stream is not altogether by the thoracic duct.

The students always ask why does fat have to go that way. Is it just to prevent the liver from having the first crack at the fat as it does at other materials which are absorbed into the portal vein? The answer is that we don't know. But it is apparently true that the absorption is almost entirely, except for some of the very short chain fatty acids, into the lymph system.

The fat is carried in the blood, we really don't know how, but possibly as a mixture of cholesterol esters and lipoproteins. What we thought was knowledge of the significance of the phospholipids has now evaporated and we tend to place greater emphasis on the lipoproteins and cholesterol esters as the vehicles by which fat is

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carried. We now think the evidence is conclusive that the fat does not have to go to the liver and that it can be deposited directly in adipose tissue. Adipose tissue is very much more active than we used to think. You can study it in vitro and it forms glycogen and fat. It responds to some of the hormones—adrenaline and insulin for example.

Carbohydrate can be turned into fat not only in the liver but in a variety of other tissues. The fat deposits are built up in the adipose tissues all over the body, stored in the relatively dry form to provide a high energy which we know is double that of carbohydrate or protein. But we have to admit we do not know exactly how fat gets into or out of the cell. We do not know the actions of the various stimuli which force it out of the cells. We do know of course a lot of conditions under which fat is mobilized. Fasting is the first one which comes to our minds. I was just asking Dr. Lukens how long an animal without its pituitary and pancreas could fast. Since its metabolism is low, it should be able to fast longer than a normal animal. It apparently cannot, although it fasts more slowly as it were, and the fat is mobilized more slowly. We have all heard the classical description of diabetes which is fasting in the midst of plenty—and it is literally true because almost all the signs of diabetes may be seen in the fasting state. It may be that many of the influences which produce diabetes are also existing in a somewhat modified form in fasting. The insulin content of the pancreas sinks to a quarter or a third or even less of its normal level. Some of the enzymes, phosphorylase for example, do not work as actively in fasting as they do in the well-fed animal. And then we have this mobilization of fat and other materials, the ketosis and many other similarities between diabetes and the fasting state.

It was Minkowski who showed the accumulation of fat in the liver in pancreatic diabetes. He saw a very fatty liver in depancreatized dogs—30 per cent fat, a big yellow liver. This was the first thing that interested me in fat metabolism apart from the magical disappearance of ketonuria after insulin. The big yellow liver of the depancreatized dog which disappeared when we gave insulin arrested my attention. Where the fat goes I don't know. It might be utilized, it might go back to the depots but the liver becomes red and lean again instead of big and yellow and full of fat.

The anterior pituitary plays a role in fat mobilization apart from the diabetogenic effect. You can mobilize fat in starvation much more rapidly by giving growth hormone or corticotropin. But we don't know the fat mobilizing hormones of the pituitary. It may be a substance which has not yet been identified, but it is associated with corticotropin and the crystalline growth hormone. By labeling fat in the depots you can show that it goes in part to the liver in fasting. The fat disappears more rapidly than in starvation if you give these pituitary materials. Fat mobilization is slowed in the adrenalectomized animal but the adrenal cortical hormones do not have as dramatic effects as the pituitary factors do.

I cannot say that we are more interested in the dietary control of fat mobilization than the hormonal, but choline and its precursors do have a very interesting part to play. Within a few hours of removing choline from the diet, you get the beginning of a fatty liver. Imbalance of amino acids or deficiency of total protein leads to the accumulation of fat in the liver. This fat deposition is not prevented by choline. Low protein fatty livers rarely exceed a value of 15 per cent of the net weight while with low choline values two or three times as great are obtained. Cirrhosis has not been produced as yet by low protein diets in the presence of adequate choline. It is obvious that protein should be supplied for the repair of liver tissue and if this protein contains sufficient amounts of the choline-precursor methionine, additional choline will be unnecessary.

MODERATOR GURIN: Dr. Best, you spoke of one point which has interested me very much—the conversion of carbohydrate to fat. Dr. Weinhouse and I have both presented the broad outlines of the pathways involved in the conversion of carbohydrate to fat by way of pyruvate to acetylcoenzyme A and on up to fat. This may be very much of an over-simplification but at least in a rough way I think it indicates what most of us believe to be the major pathway of synthesis. Now, as to what other factors are necessary for conversion of acetylcoenzyme A on up to fat is not certain. It certainly appears that one has to have normal carbohydrate metabolism; the whole glycolytic cycle appears to be necessary for the conversion of acetylcoenzyme A on up to fat. For synthesis, you have to provide energy whether it is high energy phosphate or whether it is the production of enough available hydrogen. This is, after all, a reduction synthesis when you go from acetylcoenzyme A to a fat; you have to put in a lot of hydrogen. I feel that this is a big blank at the moment.

One point has occurred to me. There is a great deal of misinformation it seems about the reverse process, namely the conversion of fat to carbohydrate and I am afraid that many of us who have worked with labeled compounds of isotopes have in a sense contributed to that error. I think Dr. Stadie might discuss this point.

DR. STADIE: This problem of fat to carbohydrate is an old one as you know. The older literature discussed only two hypotheses which could explain diabetes and they were summarized in slogans—a rather convenient way of summarizing scientific advances from time to time. You know these old hypotheses of under-utilization versus overproduction. The advocates of the overproduction theory were met by the necessity of postulating that fat went to carbohydrate. If you don't have under-utilization of glucose in diabetes you must have production of carbohydrate from fat. The controversy raged through the literature for years and years and has not yet completely vanished. The reason for this rests upon experiments done with isotopic carbon. Briefly, these experiments are as follows: When a variety of compounds, for example, acetic acid or one of the higher fatty acids labeled with radioactive carbon (C^{14}) were fed to the mammalian organism, some of that C^{14} originating from these substances showed up in carbohydrate from the isolated glucose or glycogen. This was interpreted to support the fat to carbohydrate hypothesis. But the reasoning behind this conclusion is erroneous because certain facts are neglected.

As Dr. Gurin explained, pyruvic acid has the ability to condense with carbon dioxide and form a four-carbon acid. Now that four-carbon acid is characterized by having a carboxyl at either end. All of the acids in the Krebs' cycle are dicarboxylic acids with carboxyls at either end. That represents a unique feature.

It is the oxalacetic acid which initiates the Krebs' cycle. Without that, presumably fat does not burn or burns very inefficiently; nor can it be synthesized in any direction. Now let us look at acetic acid for a moment. How can acetic acid go to fat? By condensing with the oxalacetic acid thus forming carbon dioxide as Dr. Gurin showed. In turn the carbon dioxide may condense with pyruvic acid and hence part of the fatty acid has gone to carbohydrate. But pyruvic acid is necessary for the reaction and it can only come from carbohydrate. In other words, no new net carbohydrate formation from fat has occurred. You can say the same thing in another way. Acetic acid cannot combine to form a dicarboxylic acid. This so-called Thunberg reaction has never been demonstrated in mammalian tissue. In other words, one molecule of pyruvic or oxalacetic acid originating from carbohydrate is necessary to transform a fatty acid by way of carbon dioxide to carbohydrate—there is no net gain.

QUESTIONER: Dr. Gurin, I'd like to ask Dr. Best a question. He mentioned the pituitary as diabetogenic. Is there any research to show that there is hyperfunction of this gland during diabetes?

DR. BEST: There has been little or no evidence of the production of diabetes in human beings by the pituitary growth hormone. The clinical illustration which is usually cited is, of course, acromegaly; as I remember the figures, about 17 per cent of acromegalics have diabetes and some 30 per cent may show some disturbances in carbohydrate metabolism with simple or complex sugar tolerance tests. The remarkable thing to me is that there are 70 per cent or more acromegalics who do not have diabetes. In these, the apparently established hypersecretion of the growth hormone has not led to any real sign of the diabetic state. This situation is confused because there is not very good evidence that the pituitary growth hormone made from animals' glands causes growth in the human being. We are only at the beginning of the work in which growth hormone crystallized from one species and given to the same species has been investigated carefully. I suppose to answer this question you would have to give human growth hormone to the human being to see whether it causes growth, and then if given in excess, causes the diabetic state. Such experiments have not been done. There is plenty of evidence that the pituitary growth hormone made from beef glands stimulates and eventually injures the islands of Langerhans in the dog and that it causes interference in the utilization of carbohydrate in tissue. Those experiments are satisfactory but the facts which you would like to derive from them and apply to man are not yet available.

DR. LUKENS: Dr. Best is familiar with one other fact that is worth emphasizing to physicians who observe these patients with diabetes. Namely that experimental pituitary diabetes is produced by a short course of this pituitary extract and yet the diabetes may be permanent. Now, in the late or permanent phase, there will be no evidence of pituitary overactivity and consequently in answer to that question, the pituitary overactivity may not be demonstrable even if it has been the cause.

QUESTIONER: Dr. Lukens, what is the status of high caloric feeding, especially protein, in cirrhosis of the liver?

DR. LUKENS: Anybody with cirrhosis of the liver should have a high protein diet as long as he can tolerate it well and seems to get some benefit from it. But when the disease is very bad there is the danger that that very diet which has been beneficial in the milder stage may precipitate hepatic coma. Davidson of Boston has given evidence of this. So, the question remains a matter of

clinical judgment. The high protein diet should be used as long as it is beneficial, but one should be prepared to modify the regimen when necessary.

DR. BEST: There is no evidence in animals that you can get cirrhosis of the liver with a low protein diet if choline is made available. I do not know of any condition which choline cures except choline-lack. Choline administration cannot cure amino acid deficiency. All adequate diets in this country and Canada contain plenty of choline. It is true that in animals you can produce a full-blown Laennec's cirrhosis of the liver by choline deficiency, but we have not produced it by protein deficiency if we have an abundance of choline. I think that if one is studying choline deficiency one should have adequate protein in the diet. This is difficult because methionine makes choline and yet you have to have methionine in the diet. That is the impasse we are in. Clinically, I would recommend that you provide a diet adequate in protein in cirrhosis and only supplement that diet with methionine and choline if you cannot give an adequate amount of protein for any reason.

QUESTIONER: Since it has been stated that growth hormone interferes with the utilization of carbohydrate in the peripheral tissues, how do you account for the utilization of carbohydrate in the peripheral tissues when adrenal cortical steroids are used?

DR. BEST: I made the statement that there is failure of utilization of carbohydrate in peripheral tissues after growth hormone. You can give growth hormone and demonstrate decreased utilization of carbohydrate in several tissues. I might suggest, Mr. Chairman, that Dr. Lukens or Dr. Stadie might discuss this subject better than I can.

DR. LUKENS: The usual demonstrations of the insulin antagonistic effects of growth and adrenal hormones consist of such things as the inhibition of the action of insulin, the diabetic sugar tolerance curve and so forth under their influence. It is easy to make that statement and if that answers your question, it is the sort of evidence I would offer. We do not know the biochemical mechanisms involved in such things as disturbed glucose tolerance tests.

DR. STADIE: I should like to bring up the question of this balance between the pituitary and insulin. So far as peripheral utilization of carbohydrate is concerned it is certainly possible to demonstrate in a hypophysectomized rat, for example, that the removal of the pituitary greatly enhances the action of insulin. The effect can be demonstrated with concentrations of insulin which in the normal animal will produce no reaction whatever.

DR. LUKENS: I shall try to give a factual illustration also. The depancreatized cat requires 10 to 20 units of insulin a day to maintain it; the Houssay animal equally without insulin requires one half a unit a day for equally good maintenance.

QUESTIONER: Dr. Best, assuming as you stated, that the growth hormone is diabetogenic, how do you account for the fact that testosterone which apparently works through the pituitary in an anabolic way does not cause diabetes?

DR. BEST: I think it was mentioned earlier today that Dr. Lukens said that testosterone has no anabolic reaction, but Dr. Sirek and I could find no nitrogen-retaining effect in the complete absence of the pancreas. On the other hand, by the indirect methods available, we could find no evidence that testosterone stimulated the liberation of insulin. The conclusion had to be that some insulin was necessary for the anabolic effect of testosterone. As to the action of testosterone through the pituitary, I don't know what the evidence is that testosterone causes a significant liberation of growth hormone. I am not challenging the statement, but I don't know the evidence.

DR. LUKENS: All these anabolic hormones seem to depend upon the presence of insulin, but we don't always know how much insulin is needed. In the second place, the metabolism takes place in different tissues. For example, testosterone which may cause a little growth at first in an adolescent child, actually causes closure of the epiphyses and will eventually terminate growth. In fact that is one of the reasons we give it cautiously. Nitrogen retention may be accounted for by various tissues. It is known that the genital tissues and the muscles maintain nitrogen particularly under the influence of testosterone. This is not the same as growth stimulated by growth hormone. Until all those things are understood I think it is very difficult to get any more of an answer.

DR. BEST: I should like to hear Dr. Lukens or the whole Philadelphia group discuss this point. You state that fat synthesis occurs in the Houssay animal as briskly as in the normal animal. You interfere with fat synthesis by taking out the pancreas and you restore it by taking out the pituitary. That seems very peculiar to me since the metabolism of the Houssay animal is lowered. The Houssay animal is a frail thing. How does it do so well in synthesizing fat from sugar?

MODERATOR GURIN: May I discuss this before Dr. Lukens replies? I think one point ought to be made quite clear. We are not studying the synthesis of fat when we study the incorporation of radioactive acetate or

radioactive pyruvate or anything else in fat. We are actually measuring the rate of incorporation of those carbons into fat within a given period of time. In other words, if we are dealing with a series of reversible reactions one may end up with no more fat at the end of the experiment than one started with. What these experiments imply is simply that the valve is open, that these carbons can get into fat, but it has nothing to do with the total amount of fat being synthesized or with net synthesis. This is a matter of removal of end products or the laying down of insoluble products. This is the physiological side of the story. Isotope experiments simply tell you something about the rate of incorporation. They tell you nothing about the rate of breakdown of the product or very little, so that in most instances it does not have any reference to the total amount being laid down.

DR. STADIE: This gives me an opportunity to discuss a favorite topic. There is enough evidence in the literature to back up the concept which I shall now describe. Namely, that in the mammalian organism there is a sort of primitive metabolism in which enzymes engage. But among this enzymatic level there is superimposed a hormonal control by means of insulin, the pituitary and the adrenal secretion.

The interplay of these hormones with the enzymes establishes a type of metabolism which meets the stress and demands of mammalian activities.

DR. BEST: I am very grateful to our Chairman, Dr. Gurin, and to Dr. Stadie for giving me a more *physiological* outlook than I had before. But the remarkable thing is this balance at a lower level of metabolism which you get with both the pituitary and the pancreas removed. You get another balance of course when you give large doses of growth hormone and balance them with insulin. This is a balance at a higher level than the normal with no diabetes. Huge doses of growth hormone and insulin may be given to the intact animal and the balance may be maintained. I think that some of the experiments on Houssay animals have been misinterpreted. The correct interpretation has been given by Dr. Gurin, but it has been concluded by others that quantitatively the normal interchanges are restored when both the pituitary and pancreas are removed.

DR. GURIN: I think this points up my opinion that isotopic experiments are treacherous. Not only must the experiments be carried out with extreme skill and care, but nothing is more difficult than the correct interpretation of the results.

QUESTIONER: I should like to ask if insulin is anabolic in the intact animal, that is in the absence of insulin deficiency.

DR. LUKENS: When insulin is administered to the normal person some nitrogen retention can be demonstrated, if the experimental condition is just right. In other experimental conditions it cannot be demonstrated and by and large, insulin is only anabolic when there is ample carbohydrate on which that insulin can work and which the insulin can direct into appropriate pathways for the provision of energy.

MODERATOR GURIN: Dr. Stadie, would you add to that?

DR. STADIE: Just a brief comment. There is excellent evidence in the literature that using isotopic amino acids and following their incorporation into proteins, it is possible to demonstrate a significant effect of insulin in the intact animal.

DR. BEST: Of course, when you give insulin to a normal animal it may no longer be present in physiological amounts. It is then a pharmacological substance. There is an interesting mathematical relationship in the diabetic between the dose of insulin and the retention of nitrogen. As Dr. Lukens said, this is not seen in the normal animal except under very special conditions. You also have the fact, true for all hormones, I suppose, that exogenous insulin suppresses endogenous insulin production so you really don't know what the actual amount of available insulin is.

MODERATOR GURIN: I'm just naïve enough to interpret this as really reflecting the protein-sparing action of carbohydrate. I was reminded of this when Dr. Lukens spoke of experiments dealing with increasing amounts of insulin and increasing nitrogen retention; does this simply make available more carbohydrate for the sparing of protein? Dr. Lukens, does that make sense to you?

DR. LUKENS: Yes, that is the way it seems. I once put it that insulin cannot make bricks without straw and it apparently cannot synthesize protein without some carbohydrate.

QUESTIONER: Dr. Best, does heparin have an important role in normal fat metabolism?

DR. BEST: The methods which have been developed for estimation of heparin in blood are very delicate and you can give an amount of heparin which causes no change in the coagulation of the blood and yet be able to estimate this quantity by the method of Monkhouse and Jaques. But by these same delicate methods it has not been possible to demonstrate any heparin in normal blood. Just recently evidence has been presented that heparin in a combined form is present in normal blood. It is present in tremendous excess—you can crystallize it from blood

—in anaphylactic shock in a dog, but that is an abnormal state. The clearing action of heparin on lipemic plasma is a dramatic thing. The low-density chylomicrons disappear. The evidence is increasing that there is a fall in total fatty acids of blood. So while I think that there is not enough evidence as yet to show that heparin has a normal physiological role in fat metabolism, the subject is changing very rapidly and new knowledge may soon provide us with proof of its physiological function.

QUESTIONER: Dr. Lukens, you have stated before that patients on a low protein diet may in time exhibit fatty degeneration of the liver. Do you know whether or not patients on the rice diet of Kempner for a period of a year or more might exhibit such change? I think Dr. Kempner would probably say no.

DR. LUKENS: I would say no, too, because the diet is not very palatable and the calories are deliberately reduced and therefore the protein, little though it is, is in reasonably good proportion as it is in starvation. I think that is the explanation.

QUESTIONER: Dr. Stadie, as I understand it, you don't believe that fat can be converted into glucose. Then how do you explain the attention given "glucose equivalent of fat" in planning diets?

DR. STADIE: Perhaps you are referring to the glycerol portion of the fat which is convertible to carbohydrate. I was talking about the fatty acid portion and neglecting glycerol in my discussion.

MODERATOR GURIN: Please forgive us if we neglect the glycerol. It is so close to carbohydrate that most of us think of it as actually carbohydrate. This 10 per cent portion of the fat which is glycerol is practically carbohydrate to begin with.

QUESTIONER: Dr. Best, some years ago there was a suggestion of a possible factor in the anterior pituitary which was trophic to the islets of Langerhans. Is this factor now dismissed or is the trophic effect attributed as a secondary reaction to the growth hormone or corticotropin?

DR. BEST: I think there is no specific evidence of a hormone of the pituitary which prevents the degeneration of the islets in the way that corticotropin prevents atrophy of the adrenals and the thyrotropic hormone atrophy of the thyroid. Dr. Haist has studied the pancreas of hypophysectomized animals very intensively; the gland just stops growing. The acinar tissue degenerates very definitely and the enzyme content, amylase and trypsin or their precursors sink to a very low level. The islets do not degenerate, but they do not grow and if you could stimulate the rest of the animal to grow without the pancreas, the animal would be diabetic, but of course that cannot be done. When you get resumption of growth in a hypophysectomized animal the pancreas will grow too. At the same time I have a feeling that someday it may be shown when our methods for blood-insulin determination are better than now, that in hypophysectomy there is a frequent fall in the amount of insulin liberated. We all know that when we are studying the amount of insulin in the pancreas or studying the state of diabetes we are not really getting at one important thing we would like to know about—the beta cells. We should like to know the output of insulin per minute. At present we have no way of estimating this.

MODERATOR GURIN: Dr. Stadie would like to discuss this.

DR. STADIE: Dr. Best brought up the matter of determination of insulin in the blood. By the best method available one uses an alloxanized-hypophysectomized-adrenalectomized mouse. The mouse must be loaded up with maltose given subcutaneously. It will then respond to extremely minute doses of insulin with the lowering of the blood sugar.

QUESTIONER: Patients with organic hyperinsulinism at times demonstrate a diabetic type of glucose tolerance curve in the early portion of the curve and at other times may demonstrate a flat glucose tolerance curve. What is the explanation for this variation?

DR. LUKENS: I think that as Dr. Best said, a person's own islands take a vacation when insulin is given. Now, when a tumor is secreting insulin constantly the rest of the islands are at rest. Consequently in about 50 per cent of cases of islet tumor there is a diabetic type of glucose tolerance curve. That is to say, when glucose is given in the presence of a constant large secretion of insulin there is still no lability or no adjustment of secretion. A true tumor usually will not respond to physiological stimuli and that is the explanation I have. It may be somewhat casual. The same sort of thing happens after an islet tumor is removed. The patient has glycosuria for two or three days and then the islets which have been on vacation come back into function and that person is perfectly normal.

MODERATOR GURIN: I wonder if Dr. Weinhouse would like to say anything to start a little argument and discussion.

DR. WEINHOUSE: There is one point mentioned in Dr. Gurin's discussion which I should like to emphasize. This relates to the fundamental defect in diabetes and to what extent we can attribute the well-known consequences of diabetes to a specific biochemical disturbance.

Dr. Gurin pointed out that a lack of oxalacetate would cut off the route by which acetic acid is metabolized and under these circumstances acetic acid would have no choice but to go into acetoacetate or into cholesterol and this fits in very well with the well-known features of diabetes, namely, the disturbance in carbohydrate metabolism. There are two points which I think do not fit in with this kind of explanation. Experiments with isotopes, to be sure, may be susceptible to wrong interpretation, but it seems that such experiments have not given a clear-cut indication that the rate of glucose oxidation is disturbed to any great extent in diabetes. Furthermore, oxalacetic acid is constantly regenerated; only catalytic amounts are needed and we have many sources of oxalacetic acid besides carbohydrate in an adequately fed animal. For example, it can arise readily from aspartic acid which is quite abundant in protein and it can arise from many other amino acids particularly glutamic acid which is the most abundant of the amino acids in protein.

MODERATOR GURIN: I think what he said is certainly correct. I should point out, however, that in the diabetic we are perhaps not so much faced with a deficiency of oxalacetate from carbohydrate but that we certainly are faced with an overoxidation, an increased and accelerated oxidation of fat. I am now referring to well-known work by Dr. Stadie. It seems to me that if it is assumed that one did overwhelm the oxalacetate that is available, then the overflow of acetylcoenzyme A might well be channeled in the direction of acetoacetate.

I certainly agree with Dr. Weinhouse that there is much more work to be done to nail down a number of these points.

DR. BEST: Has any attempt been made to study quantitatively the difference between the amount of injected labeled acetate that goes to cholesterol in the normal and in the diabetic?

MODERATOR GURIN: Yes, I think Chaikoff has made quantitative studies and claims that there is increased conversion to cholesterol.

The Patient Who Controls Diabetes

The individual who escapes smallpox, diphtheria and typhoid deserves no credit, because his good fortune is largely due to governmental health regulations. This does not hold for diabetes, because freedom from it in those hereditarily predisposed depends to some extent on the individual's avoidance of that contributory factor —overweight. The control of diabetes is dependent on a rigid regimen of diet, exercise and insulin—morning, noon and night—all the length of one's days.

Half a century ago it was recognized that the exceptionally wise diabetic in middle life often lived long, and that a few such persons survived even longer with their diabetes than their contemporaries of similar age without it. To such, a bronze medal was awarded by the New England Deaconess Hospital as long ago as 1930. The bronze medal was replaced by a silver medal if the fortunate recipient increased the duration of his life to half again that expected and, exceptionally, a gold medal was given when the duration of the life expectancy was doubled. At the beginning, the responsible factors in attaining a bronze medal were chiefly the patient's common sense and will power in resisting carbohydrates. When insulin arrived, lengthening the life of the average diabetic from 4.9 to 15 years and raising the average age at death from 44 to 64 years, the granting of a medal for exceeding one's life expectancy became almost commonplace, because so many deserved it.

Then gradually the thought developed that Health as well as Life should be recognized, because although so many patients lived long, at the same time many were distressingly handicapped by serious diabetic complications in the eyes, kidneys and arteries. Thereupon in 1948, the Advisory Committee of the Diabetic Fund of the Boston Safe Deposit and Trust Company, with the artistic help again of Amelia Peabody, created the Quarter Century Victory Medal which could be awarded to those who not only lived a quarter century with diabetes but also were sound in health as certified by a physical examination, which included an expert opinion of an opthalmologist and of a radiologist.

The purpose of this Quarter Century Victory Medal was threefold: (1) It recognized the moral fiber of the patient in addition to his knowledge and use of diet, exercise and insulin, and his trust in a scientific attack upon the disease; (2) it encouraged other diabetic patients above all by the example of these individuals who had lived so long and were so healthy, and (3) the Advisory Committee felt that if the life stories of such exceptional patients were analyzed, hints for the better treatment of even millions of other diabetics could be assembled. Up to now, 46 medals have been granted.

Elliott P. Joslin, M.D., in *Postgraduate Medicine,* September 1953.

The Octogenarian Diabetic

Observations in cases of diabetes before and after the age of eighty years

Howard F. Root, M.D., Paul Barclay, M.D.,† Boston*

The Eightieth Year

If the eightieth year of age be accepted as a dividing line, we may consider in this study three groups of patients. The first group is composed of patients whose diabetes began during or after the eightieth year, a conspicuously small group. Thus, of the 5,239 patients in a 50 per cent sample of cases seen between 1939 and 1947, only twenty-nine or about one-half of 1 per cent, had the onset of age designated as eighty years or over. The second group consists of patients now in the eighth decade of life whose chances of attaining their eightieth birthday are steadily increasing. Of all patients now in the seventies, the proportion who will survive to the age of eighty is about 40 per cent. The third group consists of special patients who have reached their eightieth birthday after surviving diabetes of long duration. In reviewing a long series of diabetic patients, twenty patients were found who attained the age of eighty years or more after having diabetes at least thirty-five years.

Incidence of Elderly Diabetics

The number of elderly diabetic individuals in the community and in the hospital population is greater than ever before. The care of the aged diabetic patient has become an important problem, involving dietary management, the use of insulin in patients, frequently with serious complications affecting their vision and ability to walk. As an example of the age distribution of the hospital population of diabetes, the admissions for 1953 are shown in table 1.

TABLE 1
Diabetic admissions, New England Deaconess Hospital, 1953

	Male	Female
0-19	130	133
20-39	208	210
40-69	726	854
70-79	115	158
80-89	18	24
	1,197	1,379

It will be seen that a total of forty-two patients were over eighty years of age and 273 were between seventy and seventy-nine years of age.

Thirty-Five-Year Diabetics

A review of the statistical data of 35,000 consecutive diabetic patients in the case registry of the Joslin Clinic from 1898 to 1950 revealed ninety-six patients who had clearly and indubitably survived thirty-five years of diabetes. In this group were seven patients whose diabetes had begun in childhood. In table 2 are listed twenty patients who attained the age of eighty years or more after having diabetes for periods of thirty-five years to a maximum of forty-six years. In the group are sixteen patients who were forty-five years or younger at the onset of diabetes. Actually, in this series only 1,500 patients out of 6,000 cases seen prior to 1925 had the onset of diabetes between forty and fifty years of age. It appears, therefore, that during that period of time the chance of a patient with diabetes originating between the fortieth and fiftieth year of age attaining the age of eighty years was about one in seventy-five. Since patients in this group must necessarily have developed their diabetes several years before the discovery of insulin, the expectancy here estimated must be regarded as the most unfavorable possible. Today, the chance of a patient reaching the age of eighty years with onset of diabetes under the age of forty-five years must have tremendously improved.

What are the characteristics of diabetes which enable the patient to survive thirty-five years of the disease? In this group ten were males and ten were females. Of the group six still remained alive in 1953 at ages eighty and eighty-one. Deaths had occurred in the remainder at ages varying from eighty to eighty-six years.

In each case, the discovery of diabetes had occurred soon after the onset of characteristic symptoms of polyuria, polydipsia, and weight loss. The striking thing was that the discovery of diabetes had been promptly followed

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From the Joslin Clinic and New England Deaconess Hospital, Boston, Mass.

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TABLE 2
Octogenarian diabetics after thirty-five years

Case no.	Age at last report	Sex	Living or dead	Insulin dose units	Years with insulin	Years without insulin	Age at onset	Cause of death
2,184	86	F	Dead	16*	15	29	41	Arterial heart disease
2,312	84	M	Dead	?	12	25	47	Coronary
3,875	81	M	Living	12*	17	19	44	
7,204	80	F	Dead	20*	1	38	41	Coronary occlusion
20,766	83	M	Dead	20*	10	31	42	Generalized arteriosclerosis
23,453	84	M	Living	20†	11	25	48	
10,587	81	F	Dead	12–0–8	23	19	39	Cancer of uterus
2,287	81	F	Living	10*	24	16	41	
1,293	86	F	Dead	24–0–14	25	11	50	Congestive failure
1,553	81	M	Dead	27*	11	35	35	Coronary occlusion
2,683	85	M	Dead	32*	2	40	43	Coronary occlusion
3,553	82	M	Dead	21+17*	5	30	47	Coronary occlusion
3,789	80	F	Living	32*	9	30	43	
5,810	81	M	Dead	14–5–8	20	16	45	Pneumonia
6,392	83	F	Dead	10–6–10	18	23	42	Diabetes mellitus
10,470	83	F	Dead	28*	18	22	43	Coronary occlusion
12,974	81	F	Living	15–0–15	20	20	41	
3,016	86	M	Dead	16+40*	14	21	50	Congestive failure
928	80	F	Dead	37–0–27	17	19	43	Coronary occlusion
12,006	81	M	Living	90 u. daily	21	24	36	

by careful dietary treatment. The treatment of the period from 1914 to 1925 employed rigid limitation of calories in the diet, and this group was conspicuous for the intelligence and education of its members. It included professional people such as doctors, lawyers, and teachers. The early discovery of diabetes by vigorous treatment in the early years must be emphasized. Although it is true that every patient sooner or later used insulin, in many instances the period of treatment without insulin was from ten to forty years. The causes of death were predominantly arteriosclerotic, with coronary occlusion predominating. Amputation of the great toe and lower leg occurred in each of two patients. Six remained alive in 1953.

Diabetes in the Eighth and Ninth Decades

Diabetic patients more than seventy years of age admitted in a two-year period at the New England Deaconess Hospital have been reviewed, including patients reported previously by Miller and Marble.[2] Among the 447 patients who were seventy years of age or older at the time of admission to the hospital, 281, or 62.9 per cent, were females. Thus, females outnumbered males two to one, a fact consistent with the higher incidence of diabetes among females in the older age group and also the greater longevity of females in the general population. In table 3 a distribution according to age and sex is shown. Sixty-five were over eighty years of age, thirteen exceeded eighty-five years, and one patient had attained the age of ninety years and had had diabetes for fifteen years.

TABLE 3
Age and sex of patients at time of hospital admission, 1952-1953

Age years	Sex		No. of patients
	male	female	
70-74	90	161	251
75-79	55	76	131
80-84	18	34	52
85-89	3	9	12
90 or over	0	1	1
	166	281	447

The age at onset and the duration of diabetes are summarized in table 4. The number of patients in whom the onset of diabetes was under fifty years was only forty-eight. In this group, the duration of diabetes ranged from twenty-one to forty-four years, with an average of twenty-eight and one-half years. The duration of diabetes among the forty-seven patients with onset from fifty to fifty-four years ranged from sixteen to thirty years, with an average of twenty-two.

TABLE 4

Age at onset and duration of diabetes at time of study, 1952-1953

Age at Onset (years)	No. of patients	Duration of Diabetes (Yrs.) range	average
Under 50	48	21-44	28.5
50-54	47	16-30	22
55-59	90	11-27	16
60-64	58	7-23	12.5
65-69	88	1-23	8.5
70-74	70	1-16	4.5
75-79	33	1-15	3
80 or more	13	1-3	1.5
	447	1-44	12.5

The onset of diabetes after the age of seventy becomes steadily more rare. The peak of the curve according to the age at onset of diabetes is attained during the fifties. Among the 447 patients in this series, the onset of the disease in its clinical form was estimated at between seventy and seventy-four years of age in only 70 cases, at seventy to seventy-five years in only thirty-three and after eighty years in only thirteen cases. Actually the date of onset in other patients is usually earlier than records indicate. Symptoms at onset are often mild or absent or forgotten. More reliable dates of onset can only be obtained by annual routine examinations of the urine and the blood. This has been recommended for many years and stressed more particularly in the Diabetes Detection Drive of the American Diabetes Association during the last six years.

The average duration of diabetes among the 447 patients was 12.5 years at the time of the hospital admission. This figure may be compared with average duration of diabetes at time of death with particular reference to the advancing age at death in the various eras of treatment as shown in table 5. It will be seen at all ages that the duration of life has steadily increased. For the group with onset of diabetes over the age of sixty years, however, the average length of life had only reached 10.3 years for the period ending May 11, 1954. The great prolongation of life is naturally to be found in the younger groups with onset of diabetes before the age of forty years.

Severity of Diabetes

The usual teaching is that diabetes among the aged is "mild," for the reason that the insulin dosage is relatively small and usually glycosuria may be controlled fairly easily. Although this is true in general, so far as hospitalized diabetic patients in the older age group is concerned the insulin dose is not necessarily small and indeed cases of marked insulin resistance are well-known. As indicated in table 3, 7 patients required 100 units of insulin daily or more, only 25 of the 447 patients were discharged without insulin, and 248, or 55.5 per cent, were advised to take between 20 and 49 units of insulin daily. The insulin requirement was between 50 and 99 units in almost 12 per cent. Such insulin dosages may not be necessary in elderly patients in the community, since in this hospital group the presence of many complications and the difficulty in controlling glycosuria were the reasons for admission.

Various methods were employed in the use of insulin. Seven patients received unmodified or crystalline insulin

TABLE 5

Average duration of life subsequent to onset of diabetes among 14,603 deceased ex-patients in each of the important eras of treatment. By age group at onset.
(Experience of Elliott P. Joslin, M.D., 1897-1954)

Age groups at onset	Naunyn Era 1897 to 5/31/14		Allen Era 6/1/14 to 8/6/22		Banting Era 8/7/22 to 12/31/29		1/1/30 to 12/31/36		Hagedorn Era 1/1/37 to 12/31/43		Chas. H. Best Era 1/1/44 to 12/31/49		1/1/50 to 5/11/54	
	No. of cases	Duration (yrs.)	No. of cases	Duration (yrs.)	No. of cases	Duration (yrs.)	No. of cases	Duration (yrs.)	No. of cases	Duration (yrs.)	No. of cases	Duration (yrs.)	No. of cases	Duration (yrs.)
All ages	326	4.9*	836	6.1*	1,457	8.0*	2,695	10.3*	3,607	12.2*	3,724	13.9*	1,958	16.4*
0-9	24	1.3	61	2.9	21	2.8	24	7.3	36	10.3	58	18.5	58	21.2
10-19	39	2.7	84	2.7	56	3.4	60	7.4	79	11.4	125	16.2	120	20.3
20-39	85	4.3	215	4.9	198	8.9	275	14.4	398	16.9	444	18.8	317	21.8
40-59	126	7.0	351	8.0	800	9.5	1,457	11.6	1,901	13.5	1,970	15.1	987	16.8
60 and over	51	4.4	117	6.4	379	5.5	859	7.0	1,192	8.6	1,115	9.4	473	10.3
Unknown	1	—	8	—	3	—	20	—	1	—	12	—	3	—

*Based on cases with known duration.
Note: Deaths reported through May 11, 1954.
Prepared by the Statistical Bureau, Metropolitan Life Insurance Company.

TABLE 6
Daily insulin dose prescribed at time of discharge 1952-1953

Insulin dose (units)	No. of patients	Per cent
0	25	5.6
10-19	114	25.5
20-49	248	55.5
50-99	53	11.8
100 or more	7	1.6
	447	100.0

alone; a few received protamine-zinc insulin in a single daily dose before breakfast. Of the 422 patients for whom insulin was prescribed at the time of discharge, 365, or 87 per cent, were taking NPH insulin daily before breakfast, either alone or in combination with unmodified insulin.

The diet prescribed at discharge contained carbohydrate ranging in amounts from 140 to 200 gm., 60 to 125 gm. of protein, and 40 to 120 gm. of fat. The problems of dietary prescription need the personal interest of physician, nurse, and dietitian. The older patients, particularly those with complications and those who have been long ill, may be frequently helped by careful additions of protein to their diet. It is often surprising how much change in the patient's morale can be brought about by judicious use of selection in food, with particular reference to the total calories required in this older group, compared to younger people who are physically active, and the problems of digestion are added to the problems of constipation or the easy development of what may prove to be serious diarrhea. Lack of good chewing surfaces may be important.

The reasons for admission to the hospital included regulation of diabetes in about one-third of the cases. None of this series was in diabetic coma.

Vascular Complications

Although one in five of the patients showed no characteristic clinical lesions of arteriosclerosis as a cause of symptoms or of hospital admission, it is probably fair to say that practically every patient in this series did have arteriosclerosis.

In table 7 are summarized the chief lesions associated with vascular disease. Cerebral arteriosclerosis with clinical evidence was evident in eighty-nine patients, or 19.9 per cent, arteriosclerotic heart disease in 52.1 per cent, and peripheral vascular disease in 28.9 per cent. Many patients had more than one complication and so were included in this series under more than one heading. Chronic nephritis was present in 5.1 per cent. Among the patients with cerebral arteriosclerosis, cerebral vascular accidents occurred in forty-eight patients, or

TABLE 7
Vascular complications

Complication	Number	Patients Per cent of total
Arteriosclerosis		
1. Cerebral	89	19.9
Cerebral vascular accident	48	10.7
Other Senile deterioration	35	9.2
Other Parkinson's disease	6	
2. Cardiac	233	52.1
Coronary sclerosis (ECG)	132	29.5
Angina pectoris	16	3.6
Myocardial infarction	34	7.6
Congestive heart failure	51	11.4
3. Peripheral	129	28.9
With gangrene	51	11.4
Without gangrene	78	17.5
Hypertension (over 140/90)	267	59.7
Chronic nephritis	26	5.1
Retinitis	101	22.6

10.7 per cent. Senile deterioration was present in thirty-five patients. Six patients were recorded as having Parkinson's disease.

In 333 patients, arteriosclerotic heart disease of significant degree occurred. Myocardial infarction was present in thirty-four patients, congestive heart failure in fifty-one patients and angina pectoris in sixteen. In a considerable number, although no clinical symptoms had been present, very characteristic electrocardiographic changes left no doubt of the existence of coronary arteriosclerosis. In this older group are slight changes, such as lowering of the T waves, which seem to have special diagnostic significance. We have come to give a good deal more serious interpretation to electrocardiographic changes in the elderly diabetic than would be given to the same cases in a nondiabetic. Arteriosclerotic disease of the lower extremities was a major difficulty in 129 cases. However, it is true that in a much larger number of patients, moderate degrees of impaired blood supply due to arteriosclerosis were present. This is a finding of major importance in the so-called mild elderly diabetic patient. It is in this group that slight lesions or burns, if neglected, particularly where the foot may be partially anesthetic, may have the gravest consequences in later osteomyelitis, gangrene, and amputation.

Hypertension, including patients with blood pressure readings over 140/90, occurred in 267 or 59.7 per cent of the total series. Uremia was present in only ten pa-

tients, or 2.9 per cent, but many other patients had proteinuria of varying degrees. In many, pyelonephritis had occurred in the past. The incidence of the diabetic nephropathy in our hospital population has increased. Thus, in the year 1952 the incidence of pyelonephritis was 3.3 per cent, but in 1953 it had increased to 6.8.

Although retinitis is not primarily due to arteriosclerosis, it is a complication of major importance in diabetic patients, particularly those with disease of long duration. Its frequency appears to have a fairly direct correlation with the degree of poor control of diabetes. Among the 447 patients, it is recorded in 101 cases, or 22.6 per cent, and in only three cases is retinitis proliferans recorded. Nonvascular complications are shown in table 8, although only 93 patients, or 20.1 per cent, are recorded as having the neuropathy of moderately severe type. A very much larger number might have been included had sensory disturbances and particularly loss of reflexes or loss of vibratory sensation been considered as sufficient reason for inclusion. Actually in this group of patients, probably nearly all could be shown to have some evidence of disturbance in the nervous system. The group, included here, presented painful peripheral neuritis, paralyses of the ocular nerves, diabetic tabes with paralysis of the urinary bladder, and severe disturbance in sensation in the feet, accompanied by pressure ulcers and other severe infections of the feet. Infections of one type or another occurred in 24.6 per cent of the series. Cancer was present in 9.2 per cent and gall bladder disease in 5.6 per cent.

TABLE 8
Nonvascular complications

Complications	Patients	
	Number	Per cent of total
Neuropathy	93	20.1
Infections	110	24.6
Urinary tract	39	8.7
Lower extremities	71	15.9
Cancer	41	9.2
Gall bladder disease	25	5.6

Surgical complications were present in 102 patients, or 22.8 per cent, all of whom were operated on. In fifty-one cases, amputations were carried out as follows:

Supracondylar amputations	22
Lower leg	9
Transmetatarsal	20

Operation on the extremity was carried out with low spinal anesthesia, which has over the years proved to be safest.

Deaths in the hospital occurred in 53 patients. The causes were as follows:

Myocardial infarction	20
Congestive heart failure associated with coronary arteriosclerosis	5
Uremia from nephrosclerosis	3
Cerebral vascular accidents	11
Pulmonary embolism	4
Pulmonary infarction	1
Cancer	9
Total	53

Postmortem findings in thirteen cases are summarized in table 9.

Discussion

This series of 447 patients has emphasized to us the serious problem presented by the number of aged diabetic patients, not only in the hospital but in the general population. During these last two years in Boston under the auspices of the Diabetes Committee of the Massachusetts Medical Society, a study of the foot complications of diabetic patients in the hospitals has been carried on. During a twelve-month period, 502 patients were in a group of seven Boston hospitals as inpatients requiring surgical consultation or treatment. The average stay for the group, excluding the small number who were in the hospital for only a few days because of death, was thirty days. The average period of treatment outside the hospital was twenty-seven days. If one takes into count the long period of convalescence and the fact that in ninety patients major amputations were done, the serious character of the foot lesions and the tremendous expense of this problem in the elderly patients become more significant. The important fact in the elderly diabetic patient is the necessity for carrying out treatment with as great care as in younger patients. The discovery of so-called mild diabetes in the elderly patients should be regarded as tremendously important if the crippling complications in the legs and the eyes are to be prevented. The outstanding lesions which cause hospitalization and bring the patient to become a burden to his family are vascular, first in the legs and then in the heart. These vascular lesions, while common in the general population, are of particular importance in frequency in the younger diabetic patients as well as old. Recent studies[3] have clearly indicated that careful and continuous control of the diabetes from its onset will prevent or postpone these sequelae.

SUMMARY

A review of 4,690 hospital admissions of diabetic patients in 1952 and 1953 revealed a series of 447 patients between seventy years and ninety-one years.

TABLE 9
Post-mortem findings in thirteen diabetics

Case No.	Sex	Age	Duration of diabetes	Cause of death	Pancreas	Heart
19,716	M	73	5	Congestive heart failure and gangrenous appendicitis	Islets normal in number. Slight hyaline change	Calcification of mitral annulus
6,493	M	73	15	Myocardial infarction	Islets fibrosed—moderate hyalinization of islets	Myocardial infarction, pulmonary edema (bilateral)
19,265	F	76	1	Uterine adenocarcinoma	Hydropic degeneration of islets	Coronary arteriosclerosis + +
17,447	M	78	3	Myocardial infarction	Partial or complete hyalinization of islets	
14,232	F	77	15	Cerebral infarction	Extensive hyalinization of islets. Ectopic pancreas in ileum	Calcification of mitral valve ring
15,940	M	70	28	Aspiration pneumonia	Slight fibrosis of islets	
19,337	F	74	Recent	Cerebral infarction and hemorrhage	Numerous lymphocytes	Arteriosclerosis + +
4,203	M	83	33	Pulmonary infarction, pneumonia	Hyalinization of islets; islets fibrosed	
19,955	F	83	2	Myocardial infarction	Partial hyalinization of islets and fibrosis	Arteriosclerosis + +
7,204	M	74	15	Myocardial infarction	Partial hyalinization of islets	Pulmonary edema
13,245	F	76	12	Uremia and nephrosclerosis	Islets decreased in number; partial hyalinization	Coronary sclerosis
16,166	F	71	14	Granulomatous myocarditis and brain stem damage	Hyalinization of islets	Myocardial fibrosis

Among the 447 patients, females outnumbered males two to one. The average duration of diabetes was 12.5 years. In 116 patients, the onset of diabetes was at the age of seventy and in thirteen patients the age at onset was eighty years or higher.

Twenty patients who attained the age of eighty or more years after having diabetes for thirty-five years are discussed. Ten were males and ten were females. All had taken insulin, but in each the diabetes had been discovered before the use of insulin was possible and therefore a good many years of treatment with dietary restriction alone had been carried out.

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SUMMARIO IN INTERLINGUA

Le Diabetico Octogenari
Observationes in Casos de Diabete Ante e Post le Etate de Octanta Annos

Un revista de 4690 diabeticos hospitalisate inter 1950 e 1953 revelava un serie de 447 patientes de etates inter 70 e 91 annos. Duo tertios del 447 patientes esseva femininas. Le duration median del diabete in iste 447 casos esseva 12,5 annos. In 116 patientes le declaration del morbo habeva occurrite post le etate de 70 annos; in 13 patientes post le etate de 80 annos.

Nos discute le casos de 20 patientes qui attingeva etates de plus que 80 annos con diabete de 35 annos de duration. Dece de istes esseva masculos e 10 femininas. Omnes habeva prendite insulina, sed in omnes diabete habeva essite establite ante que le uso de insulina esseva possibile. Consequentemente illes habeva habite multe annos de tractamento con solmente restrictiones dietari.

The Action of Glucagon on the Blood Sugar in Normal and Diabetic Persons

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A highly purified preparation of glucagon, the hyperglycemic-glycogenolytic factor (HGF), has become available for clinical studies. Kirtley and others[1,2] have reported on its use both in normal and in diabetic persons. Hyperglycemia was produced in all subjects; healthy persons gave an average rise of 60 per cent in the blood sugar glucose above the fasting level, and their blood glucose fell to below fasting levels between sixty and ninety minutes after the commencement of the infusion, which continued for thirty minutes. In four diabetic patients (elderly, obese, and nonketotic) the blood sugar rise was of the same degree as in the healthy group, but the fall was slower and only reached fasting levels at the end of two hours. In four other selected diabetic patients the response to glucagon was quite different. These diabetics were insulin-sensitive (young, thin, labile, and ketotic) and in them the blood sugar rose to lower levels and fell below the fasting level at one hour. These observers conclude that the insulin-sensitive diabetic has small stores of hepatic glycogen. None of the subjects had received either insulin or food on the morning of the experiment.

It has been shown by Myers and others[3] from hepatic vein blood sugar levels in animals and man that the site of the hyperglycemic effect of glucagon is in the liver. It will be remembered that Bearn, Billing, and Sherlock,[4] by the use of hepatic vein catheterization in man, have demonstrated that these same insulin-sensitive diabetics have a greater hepatic glucose uptake than do normal subjects or stable diabetics. The young labile diabetic, then, has a liver which, under the influence of insulin, greedily stores glycogen and under the influence of glucagon has little glycogen to release.

It was decided to amplify Kirtley's experiments, utilizing somewhat different conditions. The glucagon was given by intravenous injection, and not by infusion during half an hour, in order to compare the blood sugar curves with those obtained by the Himsworth insulin-glucose tolerance curve,[5] the insulin tolerance test,[6] and the glucose tolerance curve. The four tests were done in seventeen unselected diabetic patients, none of whom had received insulin therapy, and all of whom had been at rest in the hospital for three to five days on basal diets related to their surface area and with a carbohydrate content varying from 180 to 300 gm. (57.5 per cent of total calories). The tests were performed with the patients fasting. Glucagon was also administered intravenously to three subjects without metabolic disease in order to establish a normal response for this method. The response to intravenous glucagon was then determined in three diabetic children who had already been stabilized by insulin and in whom spontaneous variations of as much as 300 mg. per 100 cc. or more in a twenty-four-hour period, as defined by Kirtley for his insulin-sensitive patients, had been observed.

Since Pincus[7] had reported a large rise in the blood sugar after glucagon in the labile diabetic who had received both breakfast and morning insulin, the intravenous injection of glucagon was made in three diabetic children not only when fasting and without insulin, but also two hours after food and insulin.

It is thought that both glucagon and epinephrine enhance the first enzymatic reaction in the liver in the conversion of glycogen to glucose, by accelerating the resynthesis of active phosphorylase.[8] Kirtley stated that there was no increase in blood pyruvate after the infusion of glucagon, and in one case there was a profound fall. This effect contrasted with the response to epinephrine, where the rise in pyruvate is attributed to the stimulation of glycogenolysis in muscle. Pincus inferred from this that glucagon and epinephrine might have different effects on at least some enzyme systems, and that glucagon acted on a muscle enzyme in inhibitory fashion. Therefore in two diabetic patients, one stable and the other labile, and in three nondiabetic patients, the effect of glucagon and epinephrine, at first separately and then together, was investigated by blood sugar response.

The amount of glucose used in the glucose tolerance

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and Himsworth tests was calculated at 30 gm. per square meter of surface area. The dose of insulin used was 0.1 unit per kg. of body weight, and the dose of glucagon was 0.01 ml. per kg. of body weight. (This amount of 0.01 ml. of glucagon contains 10 *u* and is equivalent to 20 cat-units; the amount of material in one cat unit administered intravenously to anesthetized unfed cats causes a rise in the blood sugar of 30 mg. per 100 ml. above normal within twenty-five minutes.) The epinephrine was injected intramuscularly in a dose of 0.01 ml. per kg. of body weight.

INSULIN-SENSITIVE AND INSULIN-INSENSITIVE DIABETICS

It is generally recognized that although the classification of diabetics as insulin-sensitive and insulin-insensitive has clinical validity, there is considerable overlap between the two groups, and the tests designed to distinguish between them do not forecast the ultimate insulin requirements of the individual diabetic. Himsworth and Kerr[5] described a test in which intravenous insulin and oral glucose were administered simultaneously and the resultant blood sugar curve was compared with the oral glucose tolerance curve. The insulin area (the counted squares on the graph between the two curves) and the glucose area (the counted squares between the glucose tolerance curve and the fasting blood sugar base line) were expressed as a ratio, namely I/G area. When this ratio was calculated over a period of three hours, the ratio for the insulin-sensitive group was 0.79 ± 0.11 and that for the insulin-insensitive group was 0.46 ± 0.18. The same ratio calculated for the first hour was 0.51 ± 0.11 for the insensitive diabetics and 1.34 ± 0.39 for the sensitive.

Although this work has been criticized, it has received recent confirmation by the experiments of Bearn, Billing and Sherlock[4] who by catheterization of the hepatic vein in diabetic patients demonstrated that the insulin-sensitive patients had a rapid and large hepatic glucose uptake on the intravenous injection of insulin, whereas the insulin-insensitive patients had a slower and smaller uptake.

RESULTS IN THREE NONDIABETIC PERSONS

Although the glucagon was given by intravenous injection and not by infusion during half an hour, as in Kirtley's patients, the elevation of the blood sugar was greater and the subsequent fall less steep, the peak of the 73 to 100 per cent rise occurring thirty minutes after the injection, and the blood sugar taking two hours to return to fasting levels (figure 1). In only one of the group of diabetics tested did the blood sugar rise as high as in this control group.

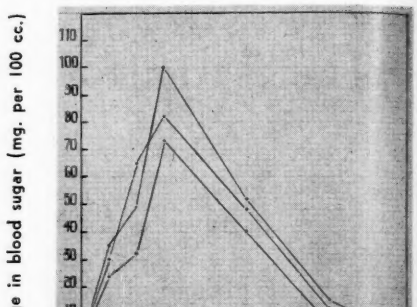

FIG. 1. The blood sugar response to intravenous glucagon (0.01 ml. per kg. of body weight) in three normal persons.

RESULTS IN LABILE DIABETICS

Three diabetic children who satisfied Kirtley's definition of instability were given glucagon intravenously; their maximum responses varied between 15 and 20 per cent (figure 2). This confirmed Kirtley's observation, and there is no reason to disagree with his suggestion that this low rise depended on defective glycogen storage. Values as low as these were, however, found in diabetic patients of a different type, as will be related below. In view of Pincus' suggestion that the available glycogen could be increased by giving food and insulin, the test was repeated in three of the children two hours after food and insulin. In two, the effect of the insulin was sufficient to offset the effect of the glucagon, but in the third child the original rise was 18 per cent when fasting and was increased to 51 per cent two hours after food and insulin (figure 5, curve 2).

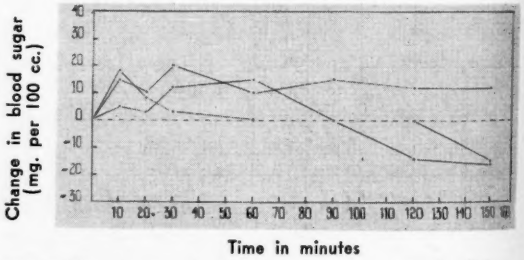

FIG. 2. The response to glucagon in three unstable diabetic children, fasting and without insulin.

RESULTS IN SEVENTEEN UNSELECTED DIABETICS

The ages of these seventeen patients were between twenty-one and seventy-four; nine of them were females and eight were males. Their weights varied between 84 and 258 pounds.

Response to Glucagon

A hyperglycemic response occurred in all cases; the blood sugar rise varied between 9 per cent and 88 per cent above the fasting level. Nine of the patients had responses of 9 per cent to 24 per cent (figure 3), and eight had responses of 25 to 88 per cent (figure 4). The ages of the first group were 58, 56, 65, 58, 59, 38, 46, and 52 years; those of the second group were 44, 45, 63, 74, 61, 49, 49, and 21 years.

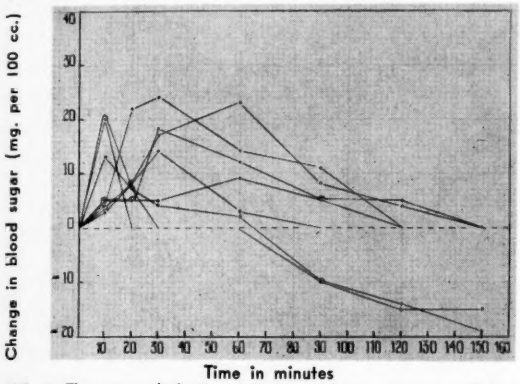

FIG. 3. The nine diabetic patients with a response of less than 25 per cent increase in blood sugar after intravenous glucagon. Note the varying rate of fall.

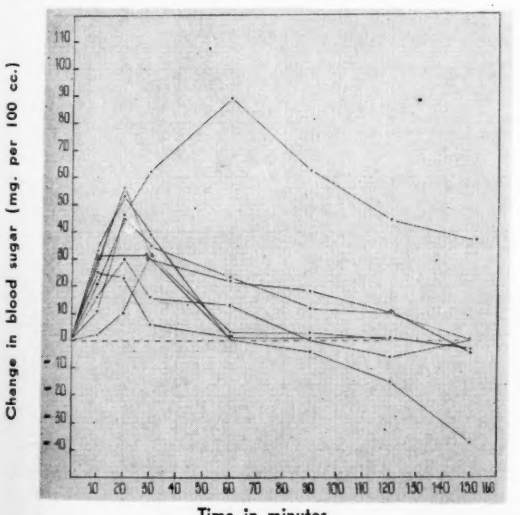

FIG. 4. The eight diabetic patients with a response greater than 25 per cent increase in blood sugar after intravenous glucagon. Note the varying rate of fall.

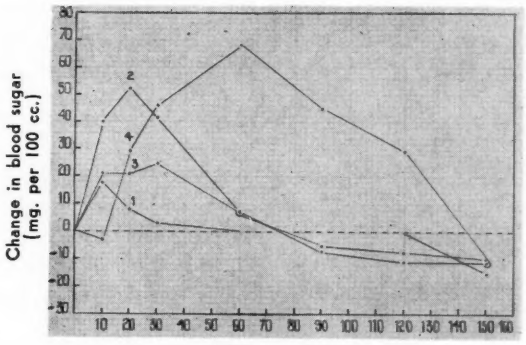

FIG. 5. C. J., diabetic child aged six years.
Curve 1—0.22 ml. glucagon intravenously.
Curve 2—0.22 ml. glucagon intravenously two hours after breakfast and 30 units of soluble insulin.
Curve 3—0.22 ml. epinephrine (1 in 1,000) intramuscularly.
Curve 4—0.22 ml. glucagon intramuscularly and 0.22 ml. epinephrine (1 in 1,000) intramuscularly.

Comment

The response to glucagon gave no correlation with age groups, but the obese diabetics tended to show blood sugar responses in the higher ranges.

Correlation with Glucose Tolerance Curve

If the blood sugar curve after the glucagon effect subsided returned to the fasting level in an hour or less, this was classified as a rapid fall; if it required more than one hour, it was classified as slow (in some cases the blood sugar did not return to the fasting level in 2½ hours). If the blood sugar in the glucose tolerance curve was more than 25 per cent above its fasting level at two hours, this was regarded as a slow fall. The correlation between the subsidence of the hyperglycemia after the administration of intravenous glucagon and after oral glucose, assessed by these arbitrary standards, was excellent. In only three cases was there any discrepancy; all these patients suffered from thyrotoxicosis in addition to diabetes, and in them the response to alimentary hyperglycemia was relatively slow, whereas the response to glucagon hyperglycemia was rapid (table I).

Comment

In general these diabetic patients responded to hyperglycemia following the administration of glucagon in the same manner as they reacted to alimentary hyperglycemia.

Correlation with Insulin Tolerance Tests

No conclusions could be drawn from comparing the height of the blood sugar after the intravenous injection of glucagon with the depth of the fall after the intravenous injection of insulin. Nor in these eight pa-

TABLE 1

Comparison of blood sugar curves after glucagon administration and in oral glucose tolerance tests

Patient		Test	Time in Minutes 0	10	20	30	60	90	120
			Blood sugar in per cent of fasting value						
L	65	Glucagon	100	120	100	100	90	85	85
		Glucose tolerance test	100	124	144	162	200	210	168
C	45	Glucagon	100	131	156	131	100	100	100
		Glucose tolerance test	100	121	162	165	214	204	200
P	58	Glucagon	100	132	132	132	100	100	100
		Glucose tolerance test	100	112	150	156	160	190	202

L: Diabetes developed some years after thyrotoxicosis had been assumed to have 'burnt out.'
C: Thyrotoxicosis and diabetes had developed coincidentally.
P: Diabetes developed while thyrotoxicosis was under control by thiouracil.

tients in whom the hypoglycemic response after insulin was more than 50 per cent over the fasting level, was there any correlation between the rapidity of the hypoglycemic action and the height of the blood sugar rise after glucagon.

Correlation with Himsworth Test

Assessed by the Himsworth test at one hour, two patients out of sixteen were insulin-sensitive and five were insulin-insensitive. The two insulin-sensitive patients, in response to intravenous glucagon, showed rises of 20 and 22 per cent above the fasting blood sugar level, whereas the five insulin-insensitive patients showed rises of 45, 13, 25, 29, and 13 per cent above that level.

Assessed by the same test at 2½ hours, six patients out of sixteen were insulin-sensitive and ten were insulin-insensitive. The insulin-sensitive patients in response to intravenous glucagon had rises of 19, 88, 20, 41, 22, and 20 per cent above the fasting blood sugar level, compared with 45, 63, 55, 19, 13, 25, 29, 13, 40, and 16 per cent, in the insulin-insensitive patients.

Assessed at the first hour, by the Himsworth test, both of the insulin-sensitive patients had responses to glucagon of less than 25 per cent and three of the five insulin-insensitive patients had responses of more than 25 per cent. Assessed at two-and-a-half hours, four of the six insulin-sensitive patients had responses of less than 25 per cent and six of the ten insulin-insensitive patients had responses of 25 per cent or more.

Comment

The Himsworth I/G ratio, determined at one hour, is probably the best clinical test for the insulin-sensitive diabetic (hepatic vein catheterization aside), and the degree of blood sugar rise after glucagon correlated poorly with this test.

RESPONSE TO ADRENALINE AND GLUCAGON IN NORMAL PERSONS

The blood sugar response to adrenaline (injected intramuscularly) and glucagon (injected intravenously) when given simultaneously was greater than when each was given separately. The time of the peak response (except in one instance) was delayed from thirty minutes or less to sixty minutes when the injections were combined (see table 2 and figure 5, curves 1, 3, and 4).

Several experiments were made to determine whether, by doubling the amount of either glucagon or epinephrine administered separately, this enhanced response and delayed peak could be reproduced. A characteristic response in a healthy person is as follows: A dose of 0.51 ml. of glucagon given intravenously caused the blood sugar to rise 57 mg. while 1.02 ml. caused a rise of 63 mg. per 100 cc., the peak response in each case occurring in 20 minutes. There was thus no marked increase of the blood sugar level when either glucagon or epinephrine was administered in double dosage. It was concluded, therefore, that the result described above depended on the combined action of glucagon and epinephrine.

TABLE 2

Maximal rise of blood sugar (mg. above fasting level) and peak time after epinephrine, glucagon, and both simultaneously

Patient	Epinephrine mg. per 100 cc.	Glucagon mg. per 100 cc.	Epinephrine and glucagon mg. per 100 cc.
Diabetic (M.T.)	+32 30	+24 20	+50 60
Diabetic (C.J.)	+25 30	+19 10	+69 60
Hypopituitary Hypogonadism (E. B.)	+75 90	+58 20	+140 60
Hypertension (O. R.)	+43 30	+73 30	+85 60
Asthma (E. B.)	+64 30	+77 30	+145 60

DISCUSSION

It is reasonable to assume, as did Kirtley, that the low hyperglycemic response to glucagon in unstable diabetics is associated with a low hepatic glycogen content. The results recounted here, while confirmatory, show that this

type of response to glucagon is not limited to the young unstable diabetic. The obese diabetic and the elderly diabetic may also exhibit this low hyperglycemic response to glucagon, even when taking diets of a high carbohydrate content. Moreover, when the hepatic glycogen content in the unstable diabetic is increased by the administration of food and insulin, the blood sugar response to glucagon may also be heightened—in one case reported here from 18 to 51 per cent above the fasting level.

Nor can anything of importance be concluded with certainty from the rate of decline of hyperglycemia. It closely paralleled the fall in the glucose tolerance curve, and, on this evidence, the hormones controlling blood sugar are no more stimulated by the injection of glucagon than by the ingestion of glucose.

Three thyrotoxic diabetics provided an exception to this observation. In all of them, the subsidence of hyperglycemia from glucagon was rapid, whereas the fall in the glucose tolerance curve was slow. This dissociation of response may indicate that in thyrotoxicosis the hepatic uptake of glucose is impeded, an effect which is not observed when hepatic glycogenolysis has followed the injection of glucagon.

The evidence produced here that the rise of blood sugar is greater when epinephrine and glucagon are injected simultaneously than when either is injected alone might be taken to confirm the suggestion of Pincus that their action, despite the experimental evidence, is on a different enzyme system. On the other hand, the fact that the blood sugar peak is delayed by half an hour suggests a continuing action on the same system, that is, a reinforced reactivation of phosphorylase. These findings do not support the suggestion that glucagon inhibits the glycogenolytic action of epinephrine on muscle.*

SUMMARY

1. Glucagon is shown to raise the blood sugar both in healthy and in diabetic persons. The hyperglycemic response to glucagon in unstable, insulin-sensitive, young diabetics is small, but it may be equally low in diabetics of other types, whether assessed clinically or by the Himsworth test.

2. The extent of the rise in blood sugar in diabetic patients is probably dependent on the amount of glycogen stored in the liver at the time of the test, and it can be enhanced by increasing the deposition of hepatic glycogen.

3. The rate of subsidence of the hyperglycemia is an individual response, since it closely parallels the fall in the glucose tolerance curve. In three thyrotoxic diabetics, however, the fall was much faster after glucagon hyperglycemia than after alimentary hyperglycemia.

4. The hyperclycemic response to epinephrine and glucagon injected simultaneously is greater than when either is injected alone, but the peak response is delayed by at least half an hour.

ACKNOWLEDGMENTS

I am indebted to Dr. W. R. Kirtley, of Eli Lilly and Company, for supplying the glucagon used in this investigation; to Dr. D. Harling, senior registrar, Drs. M. Malden, P. Griffith, J. F. Scott, P. S. Greaves, A. Maxwell, and D. B. Bower, house physicians, for their ready co-operation; to Miss M. Whyte, B.A., for dietetic advice; to Miss A. Matthews, B.Sc., Mrs. J. E. Bailey, B.Sc., Miss A. Meakin, and Miss N. Gould for the many blood sugar investigations; and to Sisters L. M. Edwards and J. E. Smedley for their careful ward control.

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SUMMARIO IN INTERLINGUA

Le Action de Glucagon Super le Sucro Sanguinee in Personas Normal e Diabetic

1. Es demonstrate que glucagon eleva le sucro sanguinee in normal e diabetic personas. In instabile juvene

*Since this article was submitted for publication, Van Itallie, Morgan and Dotti (J. Clin. Endocrinol. *15*:28, 1955) have also reported the same enhancement of glucagon-hyperglycemia by epinephrine. They suggest by a study of capillary-venous differences in blood sugar, that it is caused by the inhibiting action of epinephrine on peripheral glucose uptake.

diabeticos qui es sensibile a insulina, le grado de iste responsa hyperglycemic es basse, sed illo pote esser equalmente basse in diabeticos de altere typos, tanto quando le responsa es evalutate clinicamente como etiam quando illo es mesurate per le test de Himsworth.

2. Le grado de elevation del sucro sanguinee in patientes diabetic depende probabilemente del quantitate de glycogeno immagazinate in le hepate al tempore del test. Illo pote esser altiate per augmentar le deposito de glycogeno hepatic.

3. Le rapiditate del re-abassamento del hyperglycemia es un responsa individual: illo es satis parallel al curva de tolerantia a glucosa. Nonobstante, in tres diabeticos thyrotoxic nos constatava un abassamento multo plus rapide post hyperglycemia glucagonic que post hyperglycemia dietari.

4. Le responsa hyperglycemic a epinephrina e glucagon administrate in injectiones simultanee es plus grande que le responsa hyperglycemic a epinephrina o a glucagon injicite individualmente, sed in le caso del injection simultanee le responsa culminal es retardate per al minus un medie hora.

The Dangers of Food Faddism

Why is food faddism a matter for concern in public health? What harm does it do? We may first consider the obvious danger of direct injury to the individual both from malnutrition and from the use of deleterious drugs. For instance, the metabolic stimulator dinitrophenol has been implicated in the development of cataracts.

Food faddism is also injurious economically. Last year Herman Steen of the Millers' National Foundation, in addressing the Food and Drug Officials of the United States, cited a typical instance of financial waste—the purchase of flour at three times the regular price because it was said to be stone-ground. Many of the unusual foods consumed by faddists, though nutritious enough, are objectionable from this point of view. The nutritive value of yoghurt, wheat germ, seaweed, and so forth can be readily matched with inexpensive foods sold in any grocery store.

Another broad effect of food faddism is the general undermining of sound nutrition knowledge and practices. Agriculture, industry, and the medical and allied professions, aided by sound education and promotion, have fought malnutrition with dramatic success. But this progress is threatened and subverted by food faddism thriving on false claims and the distortions of pseudo-authorities.

False beliefs leading to undesirable food fads are of manifold origin. The sources include ancient superstition, as in vegetarianism; misinterpretation of scientific findings, as in the fear of cholesterol; and at times, deliberate misrepresentation. In their origin, nearly all food fads have one element in common—lack of facts or distortion of facts.

How best to attack the problem? Education must be our principal weapon. I should like to mention some points that might be stressed in educational programs to replace faddism with facts.

First: *The health advantages of good nutrition.* What may properly be expected of good nutrition should be explained without exaggeration or distortion.

Second: *The composition and importance of a good diet.* Many fads tend to distort the diet through exaggeration or disparagement of certain foods. We should emphasize that many dietary patterns, covering a wide economic range, may provide adequate nutrition, but that basic requirements must be met—the requirements for fuel, protein, roughage, and so forth, as well as for vitamins and minerals.

Third: *Obesity results from overeating.* In every case of overweight, it may be said unequivocally that more food is eaten than the body requires. Even if a glandular disorder is involved—and this can rarely be shown—the fact remains that a sufficient curtailment of food intake proportionate to energy output will result in weight reduction.

Fourth: *When ill, consult a physician.* The signs and symptoms of most nutritional disorders are not easily identified, and treatment should follow a professional diagnosis. Current evidence indicates that the maintenance of good nutrition promotes recovery from both acute and chronic illnesses.

W. H. SEBRELL, JR., M.D.
Federation Proceedings,
September 1954.

Mechanism of Insulin Action

Douglas R. Drury, M.D., Los Angeles, and*
Arne N. Wick, Ph.D.,† La Jolla, California

The primary action of insulin is familiar to everyone. It causes glucose to disappear from the blood. The blood sugar is in equilibrium with that in the interstitial fluid, so that when glucose is injected intravenously, it quickly distributes itself evenly in the extracellular compartment. Its passage from here into the cells is limited to a comparatively low rate. The glucose that insulin causes to leave the blood has but one place to go—into the cells.

Investigators in the past have proposed the theory that insulin primarily increases the oxidation of glucose, and that the insulin-induced disappearance of glucose from the blood was the result of increased oxidation of the glucose in the cells. Experimental work does not support this view. We can follow the behavior of the glucose molecule in the body by labeling it with radioactive carbon atoms (C^{14}). In order to carry out an accurate quantitative study of glucose metabolism, it is usually best to eliminate certain variable factors that are difficult to control, by removing the liver, pancreas, intestines, and kidney. Thus we have usually worked on the eviscerated rabbit. When an eviscerated rabbit is given enough insulin to produce a maximal effect, the disappearance rate of glucose immediately reaches a high level, with little or no further rise if administration of insulin is continued. The rate of oxidation of the glucose, as determined from the amount of tagged carbon in the expired carbon dioxide—increases slowly, and even after six hours of maximal insulin activity, only half of the disappearing glucose is being oxidized (table 1). The increased disappearance of glucose from the blood does not follow increased oxidation; the reverse is the case. Oxidation follows increased disappearance.

TABLE 1
Comparison of oxidation and disappearance of plasma glucose in an eviscerated rabbit maintained on maximum insulin

Hour	Glucose oxidized (per kg. per hr.) mg.	Glucose disappearing (per kg. per hr.) mg.
1	98	1,020
2	256	1,310
3	294	930
4	370	1,120
5	350	700
6	382	700

Another observation supports this concept. Insulin and glucose were administered for several hours to the eviscerated animal and the rate of disappearance and oxidation of glucose were determined. After five hours it was observed that 40 per cent of the respired carbon dioxide was coming from injected glucose. At this point a competitive fuel, beta-hydroxybutyric acid,[1] was injected. The rate of oxidation of glucose fell instead of continuing to rise, as it would otherwise have done (figure 1). The disappearance rate, however, continued the same as before instead of falling as it would have been expected to do if disappearance followed oxidation. These results indicate that insulin is not needed for the oxidation of glucose. This theory is well illustrated by the findings in the diabetic rat. When tagged glucose is fed to this animal its oxidation begins immediately, and within an hour, despite a large dilution of the fed glucose by body glucose, 50 per cent or more of the respired carbon dioxide is being derived from oxidation of the fed glucose. An eviscerated rat consumes much less glucose and even after four hours is utilizing glucose for only about one-quarter of its energy requirements (table 2). This difference is due to the presence of the liver in the diabetic animal. It appears that the liver changes some of the glucose to other compounds which can be more readily oxidized by the other tissues.

Presented at the Fourteenth Annual Meeting of the American Diabetes Association in San Francisco on June 20, 1954.

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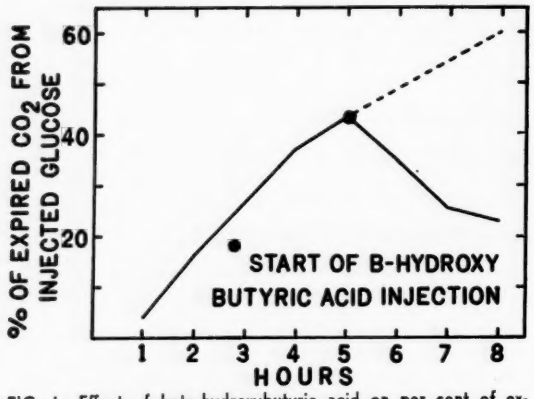

FIG. 1. Effect of beta-hydroxybutyric acid on per cent of expired carbon dioxide from injected glucose in insulinized animals. The glucose disappearance rate and carbon dioxide production remained the same throughout the experiment.

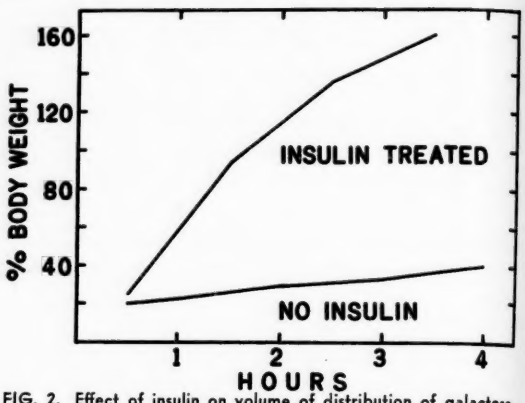

FIG. 2. Effect of insulin on volume of distribution of galactose-1-C^{14} in the eviscerated nephrectomized rabbit. No carrier galactose added. The volumes of distribution greater than total body water indicate a higher concentration of galactose in the cells than in the extracellular fluid.

TABLE 2
Comparison of glucose oxidation rates in the diabetic and the eviscerated rat

Hour	Per cent of respired carbon dioxide coming from glucose	
	Diabetic rat	Eviscerated rat
1	48	11
2	53	20
3	62	21
4	79	27

Our results support this view. If the blood of an intact rat is examined an hour or two after feeding with tagged glucose, a considerable amount of radioactivity is detected in nonglucose compounds. These compounds are ether-soluble. The molecules are probably smaller than glucose and hence quickly gain entry into the cell, so that they serve as quick fuel for the tissues. Acetic[2] and lactic acids[3] are examples of such compounds.

Such observations lead to the conclusion that insulin has little to do with the direct oxidation of glucose. Fed glucose can be quickly metabolized by diabetic animals by virtue of its being transformed into easily available fuels by the liver. Diabetic rats can derive their metabolic needs from carbohydrate, provided that they have constant access to it in their food, but they cannot store it for future needs. Glucose that has passed into the cell could also serve as a fuel in competition with other oxidizable compounds.

This view is strengthened by a report from Levine and his co-workers[4] to the effect that the intracellular transfer of galactose is accelerated by insulin. Galactose is oxidized little, if any, by the extrahepatic tissues. Insulin merely causes this hexose to be transferred into the cells, where it accumulates as a seemingly inert substance. We have obtained similar results,[5] as illustrated in figure 2. Galactose is closely related chemically to glucose, and it would appear that insulin acts on it because of this similarity. There are other sugars closely related to glucose that are also acted on by insulin. The Michael Reese workers[6] have reported that xylose is one of these. We have found that mannose also is such a sugar,[7] and furthermore that it is oxidized by the peripheral tissues, indicating that the intracellular enzymes can act on it after it is transferred into the cell. Reactivity of sugars to insulin, however, is highly specific. We have previously reported that fructose[8] and sorbitol[9] do not enter the cells in the living animal even when maximal insulin activity is induced. Data in table 3 show that gluconic acid, glucuronic acid, and 3-methyl glucose behave similarly. Figure 3 shows the structural configuration of these compounds with respect to glucose. For comparative purposes the structural configuration of the compounds that respond to insulin injection is illustrated in figure 4.

TABLE 3
Volume of distribution of glucose derivatives before and after insulin administration in eviscerated rabbits. Volume expressed as per cent of body weight. Figures in parentheses refer to time of plasma sampling after initial injection.

	Before insulin		After insulin	
Glucuronic acid	17(30′)	18(90′)	19(150′)	17(210′)
Gluconic acid	26(30′)	27(60′)	28(90′)	29(120′)
3-Methyl glucose	16(60′)	16(120′)	19(180′)	19(240′)

Recent studies of glucosamine indicate that insulin acts on it.[10] It passes into the cells much more rapidly when insulin is present (figure 5). At the same time the transfer rate for glucose is depressed. These two compounds compete in entering into the reaction accele-

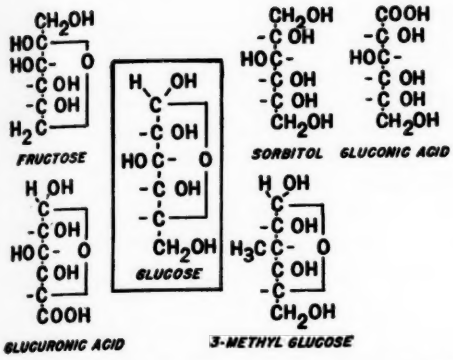

FIG. 3. Structural configuration of compounds related to glucose that do not enter the cells of the extrahepatic tissues in the living animal.

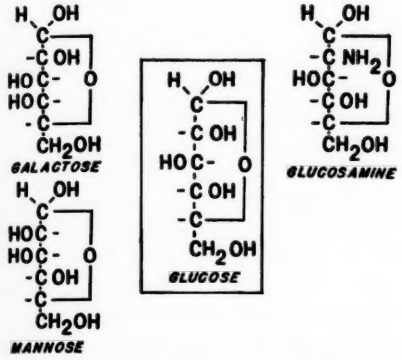

FIG. 4. Structural configuration of compounds that respond to the insulin action.

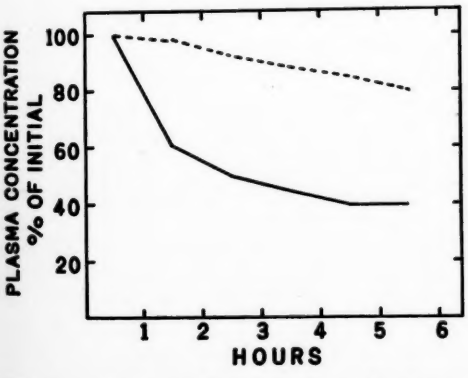

FIG. 5. Data showing the effect of insulin on the plasma disappearance of injected D-glucosamine-HCl in the eviscerated rabbit. Solid line represents an insulin treated animal and the broken line—no insulin.

rated by insulin which brings about entry of the sugars into the cells. The mechanism does not seem to be one of simple substitution. Glucosamine appears to block the process, since the entry of a given amount into the cells—for example, 100 mg.—will inhibit the entry of two to three times as much glucose. With present evidence we cannot state whether glucosamine behaves like galactose—having its intracellular transfer rate but not its oxidation rate accelerated by insulin—or whether it acts like glucose and mannose, whose transfer rate and oxidation rate are both accelerated by insulin. To answer this question will require the use of tagged glucosamine.

SUMMARY

Insulin acts on a group of compounds closely related to glucose. The effect common to these substances is an acceleration of the intracellular transfer of the hexose. With only two of these sugars, glucose and mannose, is combustion accelerated by insulin. All the data support the view that this increase is secondary to the increased amount of the sugar entering the cells.

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DISCUSSION

HELEN E. MARTIN, M.D., (*Los Angeles*): The studies made by Drs. Drury and Wick quite clearly show that the major site of insulin action is near the cell surface where in some undetermined fashion insulin effects the transfer of glucose into the cell. Their recent work on the competition between glucosamine and glucose when insulin is used is of great interest.

It has always been puzzling to understand why one diabetic patient takes three thousand units of insulin and another ten units, and why the insulin dose may fluctuate rather widely, particularly during infections and other stress situations, in the same individual. There are relatively few substances that directly antagonize insulin action which can be measured. Glucosamine may be such a substance. It is present throughout the body, as an important constituent of polysaccharides. The polysaccharides occur in many substances, such as thrombin, prothrombin, heparin. Bacterial antigenic properties are largely due to polysaccharides, of which glucosamine is a very important constituent. Also, it is the prosthetic carbohydrate combined with protein, in the well-known mucoproteins that are assuming such importance. Mucoprotein is presumably the substance laid down in the glomerular capillaries in the Kimmelsteil-Wilson lesion.

There have been some studies that have shown that glucosamine may reach levels around 100 mg. per 100 cc. in the blood. It has been shown to be elevated in diabetic renal disease and nondiabetic renal disease. Thus, it is very tempting to the clinician to speculate about the role of this substance acting as a competitor to glucose. This idea of competitive situations in the body is one that is being studied increasingly in many areas—such as in the renal tubular transport mechanisms. It may well be that there are important competitive mechanisms at the cell surface.

I would like to ask Dr. Drury to elaborate further on what to me is a very puzzling difference between the untreated diabetic rat who apparently can use glucose with a good deal of ease and very rapidly, as compared to the untreated diabetic dog who can use very little glucose, and is unable to get it into the liver or use it as a quick fuel, or the severely diabetic man who certainly is unable to use glucose quickly without insulin.

JOSEPH M. LOONEY, M.D., (*Boston*): As is well-known, the action of insulin is on the phosphorylation of these compounds. I wonder if the authors have studied the phosphate metabolism of the blood along with these changes in their sugar.

ARNOLD LAZAROW, M.D., (*Minneapolis*): I should like to ask Drs. Drury and Wick if they have evidence for action on the liver itself.

DOUGLAS R. DRURY, M.D., (*San Francisco*): Regarding the action of insulin on the liver, we have not studied it directly, and I do not know of any work by other workers that indicates any direct action of insulin on liver slices. We have not studied phosphate metabolism in our animals.

As to the importance of glucosamine clinically, knowledge of the substance is too recent for one to form a definite opinion. I know of only a few clinical articles on it. One trouble is that the authors have not distinguished too well between free glucosamine and combined glucosamine. There seems to be plenty of combined and polymerized glucosamine in the body. I doubt that free glucosamine could exist in a very high concentration in the body, because the liver would change it over to other compounds.

As to metabolism in the diabetic dog: All the diabetic animals have their own way of doing things, and the diabetic dog is certainly different from the diabetic rat. That, of course, is not to say that the primary action of insulin is any different in the two. The different manifestations of diabetes in the two animals may be due to some primary defect to which the two animals respond in different ways. There are, I suppose, a hundred different abnormalities in the diabetic. Certainly all cannot be due to differences of a hundred different insulin mechanisms. I don't know, though, that you can say that the diabetic dog or diabetic man is not burning quite a bit of glucose. No one has studied the animals while they are being fed a high carbohydrate diet.

I think the group at Berkeley have studied the diabetic dog and have found that about 20 per cent of the carbon dioxide came from the oxidation of glucose. The liver of the diabetic dog, though, certainly in a fasting condition, is doing a similar thing to what the diabetic rat's liver is doing when glucose is fed—it is making a quick fuel for the peripheral tissues. In the fasted diabetic dog the liver makes the quick fuel, betahydroxybutyric acid, out of fat.

SUMMARIO IN INTERLINGUA

Mechanismo del Action de Insulina

Insulina age super un gruppo de compositos intimemente affin a glucosa. Omne iste substantias ha le effecto de accelerar le transferimento intracellular del hexosa. In le caso de solmente duo de iste sucros—glucosa e mannosa—le combustion es accelerate per insulina. Omne le datos disponibile supporta le conception que iste acceleration es secundari al augmento del quantitate de sucro que entra in le cellulas.

Psychologic Problems of the Young Diabetic

William B. Kennedy, M.D., Philadelphia*

The impact of the diagnosis of diabetes on a youth may be shocking. He discovers that a certain amount of freedom of action to which he had grown accustomed must suddenly be denied. With education and training, he is led to realize that he is straddling a fence on which he must learn to stay. If he fails to learn his balancing act quickly and well, he may fall to one side or the other. His adjustment to this situation is gradual, requiring almost constant attention at first, but in time becoming automatic.

Thanks to recent discoveries, the diabetic in this situation can safely be permitted much more freedom than was possible a generation ago. Immunization technics and antibiotics have removed many of the hazards of infection. Practical application of the general rules of nutrition has liberalized diet restrictions. A variety of insulin forms has reduced the annoyance of frequent injections for many. The survival of large numbers of young diabetics for ever-increasing spans of a reasonably normal life has helped to remove the fears of complications that formerly haunted these people.

A brief consideration of some of the diabetic's specific problems is in order. We can uncover little or nothing that is new or startling, but it is sometimes helpful to refresh our thinking by recollection of the old and obvious.

DIETARY RESTRICTIONS

The most trying limitations upon the diabetic are those imposed by dietary restrictions. The need for a constant although adequate diet is essential, and he is reminded of this forcibly three or more times each day. Early in his diabetic life he may find co-operation easy. If he is old enough, dietetic arithmetic may interest him. If his symptoms were severe before treatment, the relief experienced will stimulate co-operation. Sympathetic understanding of his doctor, dietitian, family, and friends is appreciated, and the will to earn this support is high. However, in time, these incentives break down. Diet planning becomes monotonous. Health again is taken for granted and a little overeating brings no disastrous results. Family and friends begin, quite properly, to treat the diabetic normally. The urge for completely normal eating returns, and we cannot expect an otherwise normally adjusted youngster to continue to impose restrictions and discipline upon himself just for the sake of being good. He is quite likely to go off his diet—either openly or secretly—not constantly but intermittently.

It is impossible to set forth the means for handling this situation in each and every patient, but a few principles can be applied. One can anticipate that deviation from the prescribed diet will occur and thus not be shocked or bothered by it. Impossibly rigid restrictions should be avoided, and co-operation sought through a reasonably liberal regime. The doctor must play the role of the helpful, understanding guide and not the punitive judge. A similar attitude by parents is essential.

INSULIN INJECTIONS

The taking of insulin usually poses few problems in the young diabetic, and children of eight to ten years or older can be trained to take over its administration completely. However, one should make insulin giving as easy and brief as possible. It is surprising that few doctors recommend the safe but simple chemical sterilization of syringe and needle rather than the time-consuming and awkward boiling. With practice the complete preparation and administration of a dose of insulin can be carried out in forty-five to sixty seconds, and the morning injection becomes less of a chore than brushing one's teeth.

It is desirable to seek the preparations of insulin which will provide maximal control with a minimal number of injections daily; a program of one injection a day carries many advantages. However, young diabetics frequently respond irregularly to large single doses of longer-acting preparations, and the comfort gained from avoiding alternating periods of hyperglycemia and hypoglycemia by a two- or even three-dose regime often compensates for the extra injections. Also, such a regime removes some of the need for precise timing of meals.

Presented in part at the Third Postgraduate Course of the American Diabetes Association in Philadelphia on Jan. 20, 1955.

*Vice Dean, and Associate in Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

HYPOGLYCEMIC REACTIONS

Hypoglycemia is a difficult problem, particularly in younger children, who may ignore or fail to recognize its early symptoms. I know of no substitute for the protection afforded by observation of such youngsters by parents and other close companions and by a program of gradual education of all concerned. Severe hypoglycemia is one of the most annoying situations met by young diabetics. It causes peculiar behavior that is sometimes neither understood nor accepted by others. One diabetic was discharged from college and refused admission to another because of an alleged attack on an elderly nurse during hypoglycemia. The admissions officer of a third college feared that this behavior might reflect some underlying abnormal compulsion that could become evident in other ways, and asked my advice. I reassured him by pointing out the peculiar actions of normal individuals under partial anesthesia, where inhibitions are removed. He himself recalled having pinched a nurse while emerging from a general anesthetic, and decided to vote for the boy's admission. Another patient, a pious individual, during hypoglycemia surprised a group of his friends by swearing at a policeman who was lending a helping hand. Such embarrassing incidents should be understood.

Deep prolonged episodes of hypoglycemia, and perhaps even frequent mild ones, carry the threat of later serious cerebral damage. However, such consequences are rare, and the attitude of the patient and his family toward insulin shock should never be one of anxiety or fear. A slight insulin reaction acts as a cheap and convenient blood sugar evaluation, and an occasional episode of this kind suggests adequate control. One must expect all kinds of unusual behavior from hypoglycemia and be surprised at nothing. Also, never deny a diabetic a prophylactic dose of some form of oral glucose or other carbohydrate when he reports early symptoms of an insulin reaction. The chances are that his suspicion is correct. And even if he is faking so as to obtain extra food, the underlying difficulty will probably not be relieved by preventing success of the ruse.

VARIATIONS IN ACTIVITIES

Limitation of activity on the part of the young diabetic is seldom justified, and where imposed it does more harm than good. It is true that his course runs smoothest when the amount of exercise is constant. This applies not only to exercise but also to other factors such as insulin and food, emotions, rate of growth, daddy's temper, sister's love affairs and a host of other things beyond complete control. There is nothing abnormal about the youngster whose energy is expended in a changeable pattern.

The patient and those who deal with him must learn to recognize and anticipate the effects of various degrees and kinds of activity, so that stability may be maintained by appropriate measures. For example, one patient determined by rough trial and error that an average set of tennis required 15 gm. of extra carbohydrate, plus or minus 5 to 10 gm. for strenuous or mild sets. He could maintain control sitting at a desk in school during the week, and continue adequate balance during a full Saturday afternoon of tennis by consuming orange juice or sugar lumps in appropriate amounts between sets. To deny the young diabetic any desired form of reasonably normal activity is to create a harmful situation. Cautious experiment and learning through experience provide the means for control and avoid the hazards.

ANXIETY REGARDING COMPLICATIONS

The complications of diabetes pose an ever increasing problem to the young diabetic, and the thorough education about his disease that is essential for his adjustment to it paradoxically exposes him to the knowledge of pending complications and the natural fears that are bound to come. Even the most stalwart young patient finds it difficult to suppress all anxieties about his future. To a certain extent these fears can be transformed into a stimulus toward co-operation and control. However, tension and anxiety over any situation are likely to interrupt a smooth diabetic course and to offset benefits that might otherwise come from this reaction. An optimistic attitude is essential here. The doctor, parents, and others in contact with the diabetic must avoid exhibition of these same fears. Even an exaggerated display of hope is perfectly justified. Complications that can be avoided, treated, or compensated for must be handled expertly by both the patient and those assisting him. Those for which we do not yet have effective preventative or therapeutic devices are best ignored. The diabetic is likely to learn to develop this attitude if allowed to do so.

PROBLEMS OF CAREER

As the juvenile patient reaches adulthood he is challenged by need for adjustment to responsibilities of ever-increasing importance. The conscientious patient gives devoted thought to the various problems that arise. Should there be acceptance or denial of such things as marriage and parenthood? Can one honorably compete

for a choice career, business position or education and thereby deny that same chance to another who is more likely to offer a lifetime return on the investment made in him? Fortunately these are never one-sided decisions. The diabetic can and should be trained to be perfectly candid in his approach to such situations, and when desired opportunities result from honest dealing it is his privilege, and perhaps even his duty, to accept them. Such treasured opportunities as come his way provide an additional stimulus to maintain control of his disease.

INDIVIDUAL EMOTIONAL ADJUSTMENTS

We have considered only part of the emotional or psychological problems of the young diabetic. One cannot be definitive about means for their avoidance or control. The degree to which a diabetic is affected by such problems is dependent on many different factors incidental to each patient and his environment. The physician must recognize these variables and handle them effectively. Skilled manipulation of the scientific tools at our disposal may be wasted on a patient who does not co-operate and will not accept the relatively normal life available for the low price of a few inconveniences. The physician's responsibility to his youthful diabetic patient includes efforts to develop in him, his family, and his friends the realization that he can be a perfectly normal, well adjusted member of society with nothing to hide, nothing to apologize for, and very little to impede progress toward any goal that would be available were he to be free of diabetes.

REWARDS OF SUCCESSFUL ADJUSTMENT

One cannot leave this discussion without touching upon the dividends paid by a satisfactory adjustment to diabetes. Such a state requires discipline, will power, self-control, integrity, and an optimistic attitude—qualities which, in themselves, help to build good character and provide the individual with an opportunity to derive the most from life. It has often been contended that well controlled diabetic children display such qualities as health, intelligence, self-reliance and happiness to a degree above that exhibited by their colleagues whose metabolic processes are normal. It is essential that the diabetic youth be cognizant of these available rewards. However, they must not be over-emphasized lest the patient develop undesirable attitudes such as unjustified superiority and exaggerated pride.

The importance of the role of the physician in development of a normal adjustment to life by a diabetic cannot be overstressed. It is his privilege to assist in the education of the patient, his family, and his friends and to try to develop the proper adjustment in all concerned. This requires patience, understanding, affection, praise, and sympathy, as well as discipline and punishment, all in doses delicately balanced to meet the problems that arise in dealing with normal as well as diabetic children.

SUMMARIO IN INTERLINGUA

Problemas Psychologic del Juvene Diabetico

Pro le juvene diabetico le annuncio del diagnose de su morbo es frequentemente un choc. Ille trova que un certe grado del libertate al qual ille es accostumate debe esser negate.

Il non es possibile exaggerar le importantia del rolo del medico in assister le diabetico a disveloppar un adjustamento normal al situation de su vita. Il non suffice que le medico instrue le patiente e membros de su familia in re su regime dietari, le regulation del dosages de insulina, e le reactiones hypoglycemic. Ille debe assister le patiente a comprender le beneficios que pote resultar pro ille ab un adjustamento satisfactori al conditiones de su stato diabetic. Iste beneficios include autodisciplina, fortia del voluntate, energia, e optimismo. Ducer le patiente a comprender le valor de tal tractos require del parte del medico un combination de patientia, sympathia, e affection in quantitates delicatemente equilibrate secundo le varie problemas que se presenta in nostre contacto con juveniles diabetic exactemente como in nostre contacto con juveniles normal.

Syndrome of Idiopathic Hyperlipemia, Mild Diabetes Mellitus, and Severe Vascular Damage

David Adlersberg, M.D., and Chun-I Wang, M.D.,† New York*

This paper is concerned with the simultaneous occurrence of idiopathic hyperlipemia, diabetes mellitus, and severe vascular damage. The association of characteristic symptoms and signs over a period of many months to many years justifies the concept of a clinical entity.

Idiopathic hyperlipemia is characterized by milky or creamy appearance (lactescence) of the serum in the fasting state. This is caused by a very marked increase of the neutral fat content. Often but not always there is a concomitant considerable increase of serum cholesterol and phospholipids. By definition, primary hypercholesteremia differs from idiopathic hyperlipemia in the clear appearance of the serum and in normal content of neutral fat.[1] Both abnormalities of lipid metabolism may be associated with xanthoma formation. Xanthoma diabeticorum was extensively studied many years ago.[2, 3]

Idiopathic hyperlipemia associated with mild diabetes must be differentiated from the secondary (symptomatic) form of hyperlipemia occurring in severe diabetes. Secondary hyperlipemia in diabetes rarely, if ever, is associated with the very high serum lipid levels observed in idiopathic hyperlipemia. While secondary hyperlipemia is completely reversible by adequate treatment of the underlying diabetic disturbance, idiopathic hyperlipemia may be corrected, but rarely reverts to normal. A combination of both forms of hyperlipemia occurs in some cases of diabetes and results, as will be shown, in extreme elevation of all serum lipid fractions.

Presented at the Annual Meeting of the American Diabetes Association in San Francisco on June 20, 1954.

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CASE HISTORIES

Case 1. A fifty-two-year-old man had had angina pectoris and an acute myocardial infarction. He was hospitalized elsewhere six years previously because of polyuria, polydipsia, and unusual fatigability. The patient was obese (187 pounds). The blood pressure was 150/100. A skin eruption of small waxy papules was present on both forearms. Funduscopic examination revealed lipemia retinalis. The urine showed 4 plus sugar and no acetone. The blood sugar was 300 mg. per 100 ml. The serum was creamy. There was marked elevation of serum lipids. Chest X-ray examination showed moderate enlargement of the left ventricle. The electrocardiogram was characteristic of an old posterior wall infarction. Biopsy of the skin revealed foam-cell accumulation characteristic of xanthoma.

Following a low-fat, low-calorie diet for four weeks, there was a weight loss of 12 pounds, marked improvement of all symptoms, and a marked change in chemical findings (table 1).

Five years later the patient was admitted to another hospital because of a toe infection, thirst, and polyuria. There was eruptive xanthoma of both forearms and a healing paronychia of the right big toe. The urine contained 3 to 4 plus sugar and no acetone. Kidney function tests, blood counts, blood urea nitrogen, and electrolytes were within normal limits. There was questionable lipemia retinalis. The basal metabolic rate was normal. The electrocardiogram remained unchanged. The patient again presented a marked increase of all serum lipid fractions as well as gross lipemia (table 1). Following treatment with a low-fat, low-calorie diet, there was marked clinical improvement and reduction of all serum lipids and of serum turbidity but not to normal.

After an interval of sixteen months, the patient returned with a furuncle in the right axilla, thirst, and polyuria. He had been on an unlimited diet and had regained considerable weight. Physical examination revealed blood pressure of 150/90 and numerous waxy papules of eruptive xanthoma on both forearms. Glycosuria was 4 plus, without acetone. He was again treated with a 1,200-calorie, low-fat diet, which resulted in a weight loss of 9 pounds. The blood sugar fell to 148 mg. per 100 ml. The tests of the urine for sugar were 0 to trace. The xanthoma disappeared and there was marked improvement in the general condition.

The patient's father and mother died at forty-seven, the latter from a heart attack. A brother had no diabetes and showed a normal serum lipid partition, with total cholesterol 234, esters 187, phospholipids 246, and total lipids 705 mg. per 100 ml.

TABLE 1
Summary of data of Patient 1

Date	BLOOD Sugar mg./100 ml.	URINE Sugar %	URINE Turbidity	SERUM Total lipids mg./100 ml.	SERUM Neutral fats mg./100 ml.	SERUM Cholest. Tot./Est. mg./100 ml.	SERUM Phospholipids mg./100 ml.	Body weight lbs.	Remarks
1948									
Admission	300	4+	+++	16,000		666		187	Eruptive xanthoma Lipemia retinalis
After 4 weeks	167	Tr.	+	2,500		329		175	Low calorie diet
1953									
Admission	248	4+	+++	6,700		790			Eruptive xanthoma Lipemia retinalis (?)
After 25 days	148	0	±	1,400		393			Low calorie diet
1954									
4/16	310	4.5	+++	4,470	3,231	594/385	645	175	Free diet
4/23	247	2.8	+++	2,890	2,020	382/244	488	174½	1200-calorie diet
5/7	200	1.0	+	1,140	482	320/244	338	169¾	1200-calorie diet
5/21	148	¼	±	940		496/270		169	1200-calorie diet

Serum cholesterol was determined by the Sperry-Schoenheimer method, phospholipid by Sperry's modification of the Fiske-Subbarow method and total lipids by the Bloor method. Serum neutral fat was calculated by subtracting the figures for total cholesterol plus phospholipid from that of the total lipids.

His physical examination was normal.

Case 2. A fifty-two-year-old woman had been sterilized by irradiation in 1941. An ovarian cyst was removed in 1943. Since 1940 she had had attacks of paroxysmal tachycardia responding to intermittent medication with digitalis and quinidine. In the past four years she had had frequent attacks of anginal pain. Diabetes was discovered in 1951.

Control was attempted with diet alone and later with 15 to 25 units of regular insulin daily. Protamine zinc insulin produced severe local reactions. Diabetes control remained inadequate until 1954.

There were many cases of diabetes on the father's side. A paternal uncle and aunt died of diabetes at an early age. The mother died of heart disease at sixty-three. Many of her family had coronary artery heart disease.

The patient's weight varied between 116 and 122 pounds. The physical findings were negative. The electrocardiogram revealed old myocardial damage. The eyes, blood pressure and serum electrolytes were normal. On repeated occasions the serum was milky and showed marked elevation of all serum lipid fractions (table 2). This condition had been complicated since 1953 by eruptive xanthoma and severe diabetic neuropathy affecting all extremities.

The patient was placed on a low-fat diet and the insulin dose was raised to 50 units of regular insulin. With improvement of the diabetic status there was a radical improvement in the general condition and in the chemical findings. The xanthoma almost disappeared, and there was progressive improvement of the diabetic neuritis with subsidence of pain and marked improvement in well-being. Although the serum lipids decreased considerably and the serum cleared to a great extent, there remained a definite elevation of all serum lipids.

Case 3. A forty-nine-year-old woman had sudden loss of vision of the left eye from occlusion of the left central retinal vein three months prior to hospitalization. At that time moderate glycosuria and hyperglycemia were present, indicative of mild diabetes. There were no cases of diabetes among her blood relatives. The serum cholesterol was 880 mg. per 100 ml.

The patient was placed on a low-calorie diet and lost 20 pounds, and was hospitalized for evaluation of her condition. At physical examination she weighed 155 pounds. The blood pressure was 110/70. The fundus of the left eye was gray. The right eye was normal. The electrocardiogram showed transverse position of the heart and was otherwise negative. The urine sugar was 0.5 per cent. Serum lipid partition revealed total lipids 3,620, neutral fats 2,330, total cholesterol 692, esters 454, and phospholipids 598 mg. per 100 ml. The serum was milky. A glucose tolerance test showed a fasting blood sugar of 90 mg. per 100 ml.; the blood sugar was 175 mg. after 30 min., 165 mg. after two hours, and 135 mg. after three hours. The urine specimens had only traces of sugar.

The patient was placed on a 1,200-calorie low-fat diet, which resulted in an additional weight loss of 4 pounds in one week. There was a definite decrease in serum turbidity and serum

TABLE 2
Summary of data of Patient 2

	BLOOD		SERUM						
Date	Sugar mg. %	Turbidity	Total lipids mg./100 ml.	Neutral fats mg./100 ml.	Total cholest. mg./100 ml.	Phospholipids mg./100 ml.	Body weight lbs.	Insulin units	Remarks
9/1951	210	+++			710		123		
11/1951	243	+++			820				
1/1952	220	+++			835		120		
6/1952								10-30	
8/1952	213	+++			960			10-30	
1/1953	220	++			1,017			10-30	
6/1953	225	++			1,000			10-30	
7/1953		+++	6,500	4,550	1,050	900		10-30	
12/1953							118		Xanthoma, both elbows
3/1954			5,650	3,800	1,017	833	116	55	Xanthoma, elbows, knees, fingers. Diabetic neuritis
4/1954	178	+			730		118		
5/1954	160	+	2,500	1,620	475	405	120	55	Xanthoma disappeared. Neuritis improved.

lipids. Total lipids were 2,885, neutral fats 1,831, total cholesterol 518, esters 344, and phospholipids 536 mg. per 100 ml. The remaining marked elevation of all fractions was compatible with idiopathic hyperlipemia.

Only one daughter, twenty-eight years old, could be examined. Her serum lipids were normal: total cholesterol 202, esters 159, phospholipids 212, and total lipids 680 mg. per 100 ml. The serum was clear.

Case 4. A seventy-three-year-old man had had diabetes for many years and had been treated with 10 to 15 units of protamine zinc insulin daily. Of four children, the youngest son also had diabetes requiring insulin. Acute urinary retention occurred in December 1953; the patient was hospitalized at Lebanon Hospital and the bladder was gradually decompressed.*

Two months after a cystotomy, the patient was readmitted for a second-stage prostatectomy. He presented evidences of arteriosclerotic and hypertensive cardiac disease. The blood pressure was 180/100. He was slowly digitalized. The diabetes was only partially controlled with 10 units of insulin. There was marked lactescence of the serum and elevation of serum lipids. Total lipids were 12,400, total cholesterol 1,480, and esters 820 mg. per 100 ml. Improved control of diabetes was achieved by increasing the insulin dosage.

For two days after the prostatectomy, the patient did well, but from the third day onward his course was rapidly downhill. He had fever, was confused, could not eat, and responded with difficulty to questioning. Fluids, blood, and antibiotics were given intravenously. Despite additional supportive therapy the patient expired on the sixth postoperative day.

It is of interest that during the intervening period of half-starvation the milky appearance of the serum almost subsided and that the serum cholesterol and total lipids decreased markedly despite the simultaneous elevation of the blood sugar and urea nitrogen. The fasting blood sugar rose from 146 to 326 and the urea nitrogen from 14 to 50 mg. per 100 ml. There was a decrease of the total lipids to 8,600 and of the total cholesterol to 410 mg. per 100 ml.

Two sons and a daughter had hypercholesteremia. All were in good health and none had diabetes. None of the three children studied presented evidence of idiopathic hyperlipemia (figure 1).

Case 5. A thirty-four-year-old man was first hospitalized in Florida in September 1953 because of severe upper abdominal pain associated with nausea and vomiting. He had had repeated attacks of pain in the lower chest and upper abdomen previously and was told he had angina pectoris. In the hospital a diagnosis of acute pancreatitis was made. He was treated with three splanchnic blocks, with good effect. The serum had a milky appearance. The serum amylase was 720 units, the serum cholesterol was 680 mg. per 100 ml., and the white cell count was 16,000. The patient had known that he had diabetes since 1950. His highest fasting blood sugar was 170 mg. per 100 ml. He was markedly overweight and reduced his weight from 238 to 180 pounds in the course of two years. During his recent hospitalization 20 units of insulin were given for a few days only. There was a history of diabetes in the maternal side of his family.

The physical examination was negative except for small papules of eruptive xanthoma over the upper part of the back, neck, elbows, and buttocks. In addition, there were several pea-sized xanthomas over the skin of the posterior aspects of both lower legs. The basal metabolic rate was —12 per cent. Radiographic examination of the chest was negative. X-ray examination of the gastrointestinal tract showed a deformed duodenal cap. The electrocardiogram showed evidence of coronary sclerosis. The serum amylase was normal. On a low-fat diet, the

*We are obliged to Drs. H. Bergman and M. M. Friedman for permission to use these data.

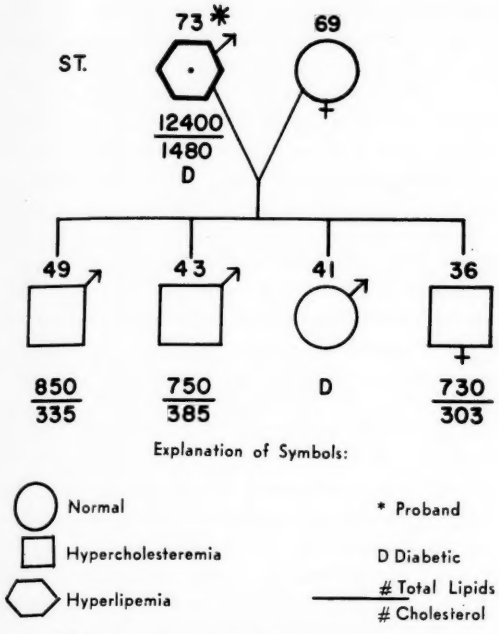

FIG. 1. Family tree of patient 4.

serum was moderately turbid. The serum total cholesterol was 249, esters 180, phospholipids 279, neutral fats 642, and total lipids 1,070 mg. per 100 ml.

The patient's brother was considered to be in perfect health. His mother presented the chemical characteristics of idiopathic hyperlipemia. Her serum was milky and the serum lipid partition was as follows: total cholesterol 414, esters 304, phospholipids 387, neutral fats 919, and total lipids 1,720 mg. per 100 ml. Except for marked obesity she was asymptomatic.

Clinical and Chemical Characteristics

The syndrome of idiopathic hyperlipemia, mild diabetes, and severe vascular damage was observed in three men and two women. Their ages ranged from thirty-four to fifty-one years. One patient (case 2) had a normal body weight; the others were moderately to severely obese. The syndrome had been known to exist in case 1 for six to seven years and in case 2 for four years. The shortest observation period was in case 4, four months, although the patient had been known to have diabetes for many years.

Three of the five patients had normal blood pressure; two had mild hypertension: 150/100 and 180/100. The kidney function was normal in all with the exception of patient 4, who had benign prostatic hypertrophy, and urinary retention and infection and died six days after a second-stage prostatectomy.

The alterations of lipid metabolism were characteristically those of idiopathic hyperlipemia. Lactescence of the serum and extensive hyperlipemia were noted in all five patients prior to treatment. The creamy or milky appearance of the serum was observed after twelve to sixteen hours of fasting and was enhanced after meals. There was marked elevation of neutral fats and of total lipids. The average level of total lipids before treatment was 8,282 mg. per 100 ml. There was moderate to marked elevation of serum cholesterol and phospholipid. The highest cholesterol level before treatment was 1,480 mg. per 100 ml.

Dietary treatment consisted in considerable reduction of calories and fats, with the use of insulin in two patients. It resulted in marked reduction of serum lipids (figure 2). The decrease affected first the serum neutral fats. The reduction of this lipid fraction was most conspicuous. The lowering of serum cholesterol and phos-

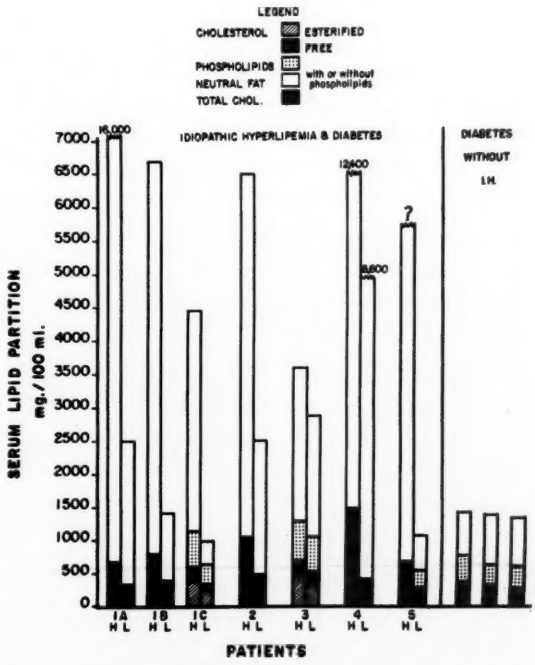

FIG. 2. Graphic presentation of serum lipid fractions of patients with idiopathic hyperlipemia and diabetes.
H = highest levels, before treatment
L = lowest levels, after treatment
For comparison, the highest lipid levels observed in three groups of diabetics presenting various degrees of control but no ketonuria and no idiopathic hyperlipemia (summarized in table 3) are shown on the right.

pholipids occurred somewhat later. The reduction of total lipids by treatment ranged from 735 to 13,500 mg. per 100 ml. and averaged 3,469 mg. for the entire group. Despite the considerable reduction of the serum lipids by diet therapy, with or without the use of insulin, the reduced lipid fractions remained above normal in most instances. These levels probably represent the "basic" levels of idiopathic hyperlipemia in these persons after the symptomatic additional elevation has been removed.

Following treatment the lactescence of the sera showed considerable reduction and the sera became sometimes clear or almost clear. As seen in other patients with idiopathic hyperlipemia without diabetes, transgressions of the low-fat diet resulted promptly in increased lactescence and elevation of all serum lipids, which lasted for several days or longer. Again this elevation affected especially the neutral fats and to a lesser extent serum cholesterol and phospholipids. The inability of patients with idiopathic hyperlipemia to clear the serum of neutral fat was evident in the entire group.

Marked additional elevation of serum lipids was seen in these cases in association with hyperglycemia and glycosuria but in absence of ketosis and ketonuria. Contrariwise, control of hyperglycemia and glycosuria resulted in decided lowering of all serum lipid fractions, probably to the basic levels of idiopathic hyperlipemia. The combination of both forms of hyperlipemia, idiopathic and symptomatic, in the same person with mild diabetes, may shed some doubt on the concept that these two types represent completely different abnormalities of lipid metabolism and are produced by different mechanisms.

For purposes of comparison we have studied lipid partitions of the fasting serum in three other groups of diabetics. They presented various age groups and various degrees of glycosuria and hyperglycemia but without ketonuria (table 3) and were thus comparable in this respect with the group of five patients of idiopathic hyperlipemia combined with diabetes. Increases in serum neutral fats and other lipid fractions were observed in patients with diabetic nephropathies and to a lesser extent in uncontrolled diabetes without manifest renal changes. There was, however, no convincing relationship in the latter group between the degrees of hyperglycemia and glycosuria and the elevation of serum lipids. The highest elevations of the serum lipid fractions encountered in these three groups of diabetics are compared with the high and low levels of the patients with idiopathic hyperlipemia and diabetes (figure 2). It is evident that the highest serum lipid levels seen in diabetes without idiopathic hyperlipemia remain far below those observed in idiopathic hyperlipemia combined with diabetes.

Another pathologic condition which may present marked elevation of serum lipids and visible lipemia is nephrosis. It must be stressed that with the exception of patient 4, who had an ascending infection of the urinary tract, these patients had normal kidney function.

The diabetes encountered in this group may be defined as mild, of the variety usually associated with moderate or severe obesity. Only two patients required insulin, patient 2, 30 to 50 units, and patient 4, 10 to 20 units. In the other cases, good diabetic control could be achieved on lowered intake of calories and fat. Diet regulation resulted in weight reduction from six to fifty-eight pounds. Patient 3 had only occasional glycosuria. She was hospitalized after considerable weight reduction; the fasting blood sugar was normal but the glucose tolerance test showed moderate diabetes. With the exception of this patient, all the subjects were members of diabetic families.

Severe vascular damage is a characteristic feature of the syndrome. It was evident in all of the five patients and to a certain extent in their families. Three patients exhibited evidence of coronary artery disease, the fourth had anginal attacks with electrocardiographic evidence of coronary atherosclerosis, and the fifth developed severe intraocular changes with occlusion of the central retinal vein and sudden loss of vision in one eye. We believe that the abnormal elevation of serum lipids represented an important predisposing factor for the severe form of

TABLE 3

Ranges and averages of serum lipids in three groups of diabetics (controls)

Group	No. of Patients	Total Cholesterol Range	Ave.	Cholesterol esters Range	Ave.	Phospho-lipids Range	Ave.	Neutral fat Range	Ave.	Total lipids Range	Ave.
1	27	155-382	253	114-282	190	194-400	267	176-683	395	625-1,435	915
2	31	132-415	258	91-295	190	163-393	270	120-747	403	415-1,390	931
3	19	131-284	201	98-204	148	188-353	254	32-717	377	420-1,340	832

Groups 1 and 2 represent ambulatory diabetics with various degrees of control but without ketosis. Complications such as retinopathy, nephropathy and neuropathy are included. Group 3 consists of younger pregnant diabetic women studied during the prenatal period. None of them had ketonuria during the examination. All figures are expressed in mg. per 100 ml.

atherosclerosis present in this group and that the diabetes might have been an additional aggravating factor. This opinion is based on observations of other patients with idiopathic hyperlipemia without diabetes, some of whom also presented evidence of severe and often premature coronary artery disease.[4]

Three patients of this group exhibited xanthomatosis of the skin. Patients 1, 2, and 5 had eruptive skin xanthoma. Patient 1 exhibited these lesions on three occasions when poor control of diabetes was associated with excessive hyperlipemia and in at least one instance with lipemia retinalis. Patient 2 had poor diabetic control for more than three years. Eruptive xanthoma and diabetic neuritis developed. Improved metabolic control resulted in subsidence of eruptive xanthoma. Patient 5 had marked intensification of eruptive xanthoma during and after an attack of pancreatitis. In addition, he had xanthoma tuberosum and was the only one in this group who exhibited acute pancreatitis. We have observed relapsing pancreatitis in three other instances of idiopathic hyperlipemia without diabetes, thus confirming the observations of Poulsen[5] and Klatskin and Gordon.[6] One may even consider the possibility that diabetes may be secondary to idiopathic hyperlipemia and pancreatitis in some instances even if a definite history of the latter is not obtained.

Although no detailed studies could be made regarding the familial character of this syndrome, there was evidence of familial hypercholesteremia in one case and familial hyperlipemia in another proband. Combination of both disorders (without diabetes) was observed by us in close relatives.[4] There was in addition a high incidence of coronary artery disease in the families.

HYPERCHOLESTEREMIC XANTHOMATOSIS ASSOCIATED WITH DIABETES

We have observed two patients with hypercholesteremia of the xanthoma tendinosum type associated with diabetes. The clinical manifestations and the abnormalities of lipid metabolism differ significantly from those of idiopathic hyperlipemia associated with diabetes.

Case 6. A forty-three-year-old woman, a known diabetic for ten and one-half years, had extensive xanthelasmas of the eyelids, xanthomas of the tendons, and only one isolated xanthoma tuberosum-like lesion over the skin of the right tibia. Following an episode of acidosis and ketosis marked elevation of all serum lipid fractions was noted. Total lipids were 2,555, neutral fats 1,509, total cholesterol 612, esters 430, and phospholipids 434 mg. per 100 ml. One month later following treatment the serum lipids were lower. Total lipids decreased to 1,375, neutral fat to 555, total cholesterol to 451, esters to 319, and phospholipids to 369 mg. per 100 ml. The serum was clear on both occasions.

Case 7. A forty-eight-year-old woman had extensive xanthelasmas of the lids and multiple xanthoma tendinosa. For the past two years there was mild diabetes, which was adequately controlled by diet alone. The serum was always clear. Total lipids were 975-1,000, a total cholesterol 273-286 and phospholipids 263-287 mg. per 100 ml.

Hypercholesterolemic xanthomatosis differs from idiopathic hyperlipemia in the clear appearance of the serum and in absent or only moderate elevation of serum neutral fats. In acidosis and ketosis additional secondary elevation of all serum lipid fractions may be observed (see case 6). There are also clinical differences between xanthomatosis with diabetes and idiopathic hyperlipemia with diabetes. While in the idiopathic hyperlipemia group only one patient presented a small pinpoint-sized lid xanthelasma, both patients of the other group had extensive lid xanthelasmas. None of the patients of the idiopathic hyperlipemia group exhibited xanthoma tendinosum, whereas both patients of the other group had multiple xanthomas of the tendinous type. Three of five patients with idiopathic hyperlipemia had eruptive xanthoma, especially during periods of hyperglycemia and glycosuria; in contrast, none of the patients of the other group presented eruptive xanthoma. It is therefore justified to separate idiopathic hyperlipemia associated with diabetes from xanthomatosis associated with diabetes on both clinical and chemical grounds.

DISCUSSION

The clinical and chemical aspects of idiopathic hyperlipemia have been less extensively studied than those of primary xanthomatosis, a more frequently occurring disorder of lipid metabolism. Our own studies were concerned with the genetic and metabolic aspects of primary xanthomatosis and its relation to atherosclerosis.[7, 8] Continuation of this work led to the observation that some members of the families under study with or without extensive xanthomatosis exhibited constant turbidity of the fasting serum and marked elevation of neutral fats characteristic of idiopathic hyperlipemia. Of twelve probands with this fault of lipid metabolism, five presented diabetes mellitus and manifestations of severe vascular damage. Continued clinical observation led to the concept that the signs and symptoms observed in these patients represent a clinical entity.

Of forty-one patients with idiopathic hyperlipemia collected from the literature by Lever and others,[9] five had glycosuria and of these three had hyperglycemia. There was considerable elevation of serum total lipids, 4,477-6,570 mg. per 100 ml., and of serum cholesterol,

693-1,040 mg. per 100 ml. The status of the diabetes is not always evident from the reports.

The five patients reported here exhibited diabetes and changes of serum lipids compatible with idiopathic hyperlipemia. They revealed, in addition, a remarkable lability of lipid metabolism in connection with hyperglycemia and glycosuria but in absence of ketonuria. Milder instances of a similar disturbance might have been observed by Hirsch and his associates.[10, 11] Hyperglycemia in their diabetic patients was associated with a marked elevation of "esterified fatty acids" of the blood; after treatment and lowering of the blood sugar level, there was a return of the lipid fraction to the normal range. Hirsch's concept of a direct relation between hyperglycemia and hyperlipemia in diabetes deserves additional studies. It may be mentioned parenthetically that in nondiabetics there is an apparent age difference in the response to ingestion of fat, characterized in the old by a prolonged elevation of serum total lipids lasting up to twenty-four hours.[12]

A comparison between idiopathic hyperlipemia associated with diabetes and hypercholesterolemic xanthomatosis combined with diabetes was of interest. Xanthelasma of the lids and xanthoma tendinosum were characteristic of idiopathic hypercholesterolemia, whereas eruptive and tuberous xanthoma was a feature of idiopathic hyperlipemia. Similar differences seem to exist between the two entities if they are not associated with diabetes.[9] Studies performed with labeled acetate and labeled cholesterol revealed biochemical differences of exogenous and endogenous cholesterol metabolism between the tendinosum and tuberosum types of xanthomatosis.[13]

In patients with idiopathic hyperlipemia without diabetes, occurrence of severe and often premature atherosclerosis was striking.[4]

The possibility that idiopathic hyperlipemia represents an important predisposing factor for atherosclerosis must be considered seriously.

Degenerative vascular disease in diabetes has been recently the subject of many studies.[14] In this connection, these observations may be of interest. The relationship between glycosuria and hyperglycemia and elevated lipid levels seen in idiopathic hyperlipemia associated with diabetes may be characteristic of extremes of disturbed lipid metabolism. Milder disturbances of a similar nature may exist perhaps more often in diabetes. A possible relationship between hyperglycemia and glycosuria (and their control) and degenerative vascular disease in diabetes may thus be mediated by the concomitant abnormalities of lipid metabolism.

SUMMARY

The syndrome of essential hyperlipemia, mild diabetes mellitus, and severe vascular damage was observed in five persons, three men and two women. Their ages were thirty-four to seventy-three years. Severe vascular damage was seen in all five patients. Four patients, of whom two had mild hypertension, exhibited evidence of coronary artery disease and myocardial infarction; the fifth had thrombosis of the central retinal vein and loss of vision in one eye. Extensive hyperlipemia was noted in all five and was characterized by persistent milky serum. There was marked elevation of both neutral fat and total lipids, with elevated levels of free and esterified cholesterol and phospholipids. Restriction of calories and of dietary fat, combined in some cases with the use of insulin, resulted in a decided gradual reduction of serum neutral fat and total lipids as well as the other serum lipid fractions. One patient exhibited severe acute pancreatitis with eruptive xanthoma. Two other patients had eruptive xanthoma which subsided with improved control of diabetes and lowering of serum lipids.

There are clinical and chemical differences between idiopathic hyperlipemia combined with diabetes and hypercholesterolemic xanthomatosis associated with diabetes. It is, therefore, advisable to separate these two entities.

Although the alteration of serum lipids observed in idiopathic hyperlipemia with diabetes represents extreme changes of lipid metabolism, similar abnormalities of a lesser degree are probably present in other diabetics.

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DISCUSSION

HENRY T. RICKETTS, M. D., (*Chicago*): I think none of us can deny that the levels of serum lipids portrayed by Dr. Adlersberg are considerably higher than one ordinarily sees in mild diabetes. Whether this group of symptoms consisting of marked hyperlipemia, mild diabetes and vascular disease, can be called a syndrome, is perhaps open to debate. I have a little inside information which I derived from reading his manuscript, and which you do not have, to the effect that, as I understood it, Dr. Adlersberg has had twelve of these patients with hyperlipemia and among those, only five exhibited the total picture he has described. In view of these facts, it might be just as well to refer to the condition as the coexistence of certain symptoms rather than a definite syndrome.

This audience, of course, is interested in knowing, or speculating upon, the role of diabetes in the production of vascular disease in the patients that Dr. Adlersberg has presented. He has stated that among his nondiabetic patients with idiopathic hyperlipemia, the occurrence of severe vascular disease is quite striking. I wonder if he can tell us how striking. In other words, what is the percentage incidence of vascular damage in these nondiabetic hyperlipemic patients? If it is nearly 100 per cent in these, then there is little room, so to speak, for the occurrence of diabetes to increase it. Consequently, the role of diabetes in producing the vascular disease in the five patients whom he has told us about, would seem to be in some doubt, while the importance of the serum lipids would seem to receive further support. I believe this is a conclusion in which Dr. Adlersberg would concur.

STEFAN S. FAJANS, M. D., (*Ann Arbor, Michigan*): I have been able to follow seven patients with primary hyperlipemia, of whom four had normal glucose tolerance tests and three had diabetic glucose tolerance tests. None of the seven has any detectable vascular disease.

I would like to make a statement about treatment of essential hyperlipemia, since in the literature one frequently finds a statement that a low caloric diet is necessary for the control of hyperlipemia. In carefully controlled studies with constant diets, we have shown that regulation of dietary fat and not of calories is important in the control of the lipemia.

For instance, in one patient, a 2,000 calorie diet containing 75 gm. of fat maintained a hyperlipemia of about 6,000 mg. of total fatty acids. An iso-caloric, low-fat diet caused a very rapid and prompt fall in the total fatty acids as well as the other lipid constituents. A low-caloric, 75 gm. fat diet caused an equally rapid rise in the total fatty acids. A low caloric, low fat diet also causes a fall in the total fatty acids.

As I stated before, none of these patients had any detectable vascular disease. I would like to ask Dr. Adlersberg whether it is not possible that in his patients it is actually the concomitant diabetes rather than the essential hyperlipemia which is responsible for the vascular disease.

DAVID ADLERSBERG, M. D., (*New York*): If one observes well defined symptoms and signs in a group of patients, follows them for years and gains the impression that these symptoms and signs are in some way correlated, I believe one is justified in using the term syndrome.

As a matter of fact these observations are not completely new. In an excellent paper on idiopathic hyperlipemia by Lever of Boston, published in the *Journal of Investigative Dermatology,* data concerning a group of 41 cases of idiopathic hyperlipemia collected from the literature are presented in a table. Although Lever did not go into the question of diabetes, a study of the table discloses that five of the forty-one patients had glycosuria and three hyperglycemia.

In regard to the vascular lesions in diabetes and nondiabetics with idiopathic hyperlipemia, I believe that we have to revise our ideas radically. Although author-

ities in this field have considered idiopathic hyperlipemia innocuous in this respect, in contradistinction to idiopathic hypercholesteremia, recent studies of others and our own observations indicate that severe vascular damage is strikingly often encountered in patients with idiopathic hyperlipemia. One should not forget that severe instances of idiopathic hyperlipemia, and those associated with advanced and early atherosclerosis are usually the severe cases of hyperlipemia, are associated with marked hypercholesteremia with serum levels up to 1,000 mg. per 100 ml. and higher.

At this time we believe that idiopathic hyperlipemia, associated with extensive xanthoma tuberosum, represents the severest disturbance of lipid metabolism while idiopathic hypercholesteremia, usually associated with xanthoma tendinosum and lid xanthelasma, is a milder metabolic error. Studies with labeled cholesterol and acetate performed by the Memorial Hospital in collaboration with our group seem to support this concept.

We have observed among twelve patients with idiopathic hyperlipemia four who were and are completely asymptomatic. This group showed, however, chemically mild degrees of the metabolic aberration and responded promptly to low fat diets. In the others who had severer degrees of idiopathic hyperlipemia and who were perhaps more resistant to dietary treatment, there was significant evidence of advanced premature coronary atherosclerosis.

I was very much interested in the observations of Dr. Fajans concerning effects of diet in idiopathic hyperlipemia. The response to a low fat diet certainly varies with the patient. It may be important to consider the calorie intake as well. A low fat diet with an otherwise normal calorie intake is probably less effective than a low fat diet containing the same amount of dietary fat but in combination with a reduced calorie intake. In other words reduction of both fat and calories are probably important factors in the dietary treatment of idiopathic hyperlipemia. Only a part of the metabolic disturbance appears to be the inability to dispose of the neutral fat of the serum.

SUMMARIO IN INTERLINGUA

Syndrome de Hyperlipemia Essential, Leve Diabete Mellite, e Sever Lesion Vascular

Le syndrome de hyperlipemia essential, leve diabete mellite, e sever lesion vascular esseva observate in 5 patientes, 3 masculos e 2 femininas, de etates inter 34 e 73 annos. Sever lesion vascular esseva notate in omne le 5 casos. In 4 patientes, 2 del quales habeva leve grados de hypertension, nos observava morbo del arteria coronari e infarcimento myocardiac. Le quinte patiente habeva thrombosis del vena retinal central e perdita del vision de un oculo. Hyperlipemia extense esseva notate in omne le 5 casos e esseva characterisate per sero persistentemente lactee. Le valores pro grassia neutre e lipidos total esseva marcatemente elevate, con nivellos elevate de libere e esterificate cholesterol e phospholipidos. Restriction del calorias e del grassia dietari, combinate in alicun casos con administrationes de insulina, resultava in un decidite reduction gradual del valores seral de grassia neutre e lipidos total e etiam del altere fractiones lipidic del sero. Un patiente exhibiva sever pancreatitis acute con xanthoma eruptive. Duo altere patientes habeva xanthoma eruptive que se attenuava con meliorate controlo de diabete e abassamento del valores de lipidos seral.

Il existe differentias clinic e chimic inter hyperlipemia idiopathic combinate con diabete e xanthomatosis hypercholesterolemic associate con diabete. Consequentemente il es recommendabile que iste duo entitates es differentiate.

Ben que le alteration del lipidos seral que es observate in hyperlipemia idiopathic con diabete representa extreme alterationes del metabolismo lipidic, simile anormalitates de grado minus notabile es probabilemente presente in altere typos de diabete.

The Conduct of a Camp for Diabetic Children

The Management of Juvenile Diabetes

Leon S. Smelo, M.D., Birmingham, and Samuel Eichold, M.D.,† Mobile, Alabama*

Summer camps for children with diabetes have gained wide acceptance as an economical means of combining (1) recreation, (2) regulation of diabetes, and (3) education.

Because of this triad of functions, the diabetic camp is set apart from the ordinary summer camp, requires a larger and more highly trained staff, and places a greater burden of work and responsibility upon those who direct it. The difficulties involved in conducting such a camp must seem formidable, for in 1954 only 25 were open in the entire United States and Canada to serve an estimated 30,000 children. The authors have prepared this article to indicate that the difficulties are not excessive and to guide prospective founders and leaders of diabetic camps. Our experience now encompasses the years 1948 through 1954 in operating Camp Seale Harris, during which the number of campers increased from 13 to 65,‡ and the staff from 6 to 34. The operating budget never exceeded $3,500.

The camp has several sources of income: (a) contributions from parents of campers and others; (b) camperships of $50.00 donated by local diabetes societies, civic groups and generous individuals, (c) fund-raising drives sponsored by persons with the welfare of the camp at heart, and (d) commodity gifts of foodstuffs, drugs, chemicals, etc. We have benefited inestimably from the generous cooperation and farsighted policy of the Girl Scout Council, Mobile, Alabama, which has allowed its excellent camp facility to be utilized for the diabetic camp upon the conclusion of its own season. Year after year more than half of the campers paid nothing or only a small portion of their expenses. No eligible child is refused admission for monetary reasons.

1. *Recreation*: Despite the necessity for diabetic management and the advisability of an educational program, a fact never to be forgotten is that recreation is the fundamental reason for conducting a camp.

The daily schedule should provide a sufficient number and diversity of activities to keep each camper busily engaged throughout the day. At times the diabetic child must be taught that he *can* play and *how* to play individually and in the group.

Herein is presented in condensed form the daily camp schedule which integrates the recreational program with the demands of diabetic care:

6:30 a.m.	— Reveille
6:30-7:15 a.m.	— Urine tests, blood sugars, insulin administration
7:15-7:40 a.m.	— Begin cabin clean-up
7:40-7:45 a.m.	— Colors
7:45-8:15 a.m.	— Breakfast
8:15-8:45 a.m.	— Conclude cabin clean-up
8:45-11:45 a.m.	— Morning activities
11:45-12:15 a.m.	— Urine tests: insulin administration
12:30-1:00 p.m.	— Lunch
1:00-1:45 p.m.	— Group instruction in diabetic care
1:45-3:00 p.m.	— Rest
3:00-5:15 p.m.	— Afternoon activities
5:15-5:45 p.m.	— Urine tests: insulin administration
6:00-6:30 p.m.	— Supper
6:30-8:45 p.m.	— Evening activities
8:45-9:15 p.m.	— Urine tests: bedtime feedings
9:15 p.m.	— Taps

During the periods assigned to activities, the type frequently is changed because of the short attention span of children. Good supervision and instruction are fostered by dividing the campers into small groups, which simultaneously rotate through a series of activities including swimming, boating, canoeing, horseback riding, hikes, picnics, riflery, archery, handcrafts, softball, basketball, and nightly campfires.

During the 1954 season attended by 65 children, this program functioned under a 34-member recreational staff, all salaried and full-time, consisting of (a) a program director, (b) a separate swimming instructor for boys and for girls, (c) a boating and canoeing instructor, (d) a riflery-archery instructor, (e) a horseback riding

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‡Two campers sent in 1954 as diabetics by their family physicians were found on study at camp to be nondiabetic.

instructor, and (f) a handcrafts instructor. Supplementing these specially qualified staff members, a counselor, assistant counselor and student nurse are assigned to each cabin to maintain discipline; to see that schedules are met; to check on diet consumption at meals, insulin administration, urine testing, and for insulin hypoglycemia, and to provide general supervision and advice for the youngsters.

2. *Regulation of Diabetes*: Regulation of diabetes during the two-week period necessarily imposed by the camp season, is attended with difficulties beyond those inherent in the well-recognized labile character of juvenile diabetes. The children are referred by many physicians with divergent concepts in regard to the management of diabetes and optimal standards of control and with varying viewpoints with regard to what they expect the camp medical directors to do. Some referring physicians expect standardization of the diabetes of children sent to camp; others will not look with favor upon any change in the mode of therapy they have previously established.

We who conduct Camp Seale Harris believe full chemical control is the only desirable level of control in juvenile diabetes. This means normal blood sugars, aglycosuria, and minimal insulin reactions on a diet adequate for normal weight and growth. In 1954 the medical staff consisted of a medical director, an associate medical director, and an intern; a camp nurse, two associate camp nurses, and five student nurses; a dietitian and appropriate kitchen staff; and a technologist and assistant; all full-time and salaried save the medical director and his associate.

To evaluate and regulate diabetes both urinalyses and blood sugar determinations were employed. On entry each camper was assigned his individually marked, quart-sized urine container to collect the entire specimen voided during four fractional periods each day to be tested at the end of each fractional period: 1. After breakfast, 7:00 a.m. to 12:00 noon. 2. After lunch, 12:00 noon to 5:30 p.m. 3. After supper, 5:30 p.m. to 9:00 p.m. 4. Overnight, 9:00 p.m. to 7:00 a.m. Occasional spot urinalyses also were done in the event of doubt about an insulin reaction and to determine a blood sugar trend. Capillary blood sugar analyses were utilized to guide adjustments in insulin therapy, to determine the adequacy of control when 24-hour aglycosuria was obtained, and to check on suspected insulin hypoglycemia. For the two-week period with the 65 campers, a total of 428 blood sugar analyses were performed.

During the initial days at camp each child's diabetic behavior was observed with diet and insulin schedule prescribed by his physician. If the diet was clearly insufficient or excessive for a youngster's weight and activity at camp, it was suitably revised. Similarly, if the diabetes was not well-controlled, adjustments in insulin therapy were made. In so far as possible, a child was maintained upon the type of insulin administered before coming to camp and an effort made to readjust the dosage. Frequently, this objective could not be attained because of the characteristics of a particular insulin.

We found NPH insulin to be the preparation most frequently prescribed for the children attending camp. With this insulin, upon injection before breakfast, the maximal permissible dose is that which establishes a normal blood sugar during the late afternoon hours, after a mid-afternoon feeding. When such a blood sugar is obtained, further increase in dose will induce hypoglycemia and must be avoided.

It was frequently noted that with the maximal allowable dose of NPH insulin a youngster exhibited one or all of the following: (1) fasting hyperglycemia; (2) glycosuria and/or hyperglycemia after breakfast; (3) glycosuria and/or hyperglycemia after supper. The first was overcome by supplementing the NPH insulin with sufficient protamine zinc insulin to reduce the fasting blood sugar to normal; then, if glycosuria or hyperglycemia after breakfast persisted, supplementary regular insulin was given with the NPH and PZ insulins. At times NPH insulin had adequate duration of action to effect fasting normoglycemia, but permitted glycosuria after breakfast. This was readily managed by supplementary regular insulin. Finally, regular insulin before supper was administered to correct post-supper glycosuria or hyperglycemia. Since globin insulin resembles NPH insulin in action, failure to secure full diabetic control with either insulin alone was similarly managed with supplementary protamine or regular insulin.

In recent months a new preparation of zinc insulin suspension, now designated "lente," has been introduced. We substituted lente insulin for the combination of NPH and protamine zinc insulins in certain instances, but did not as a rule eliminate the need for protamine zinc insulin.

Protamine zinc insulin was employed second most commonly by physicans treating our campers. A normal fasting blood sugar indicates the greatest permissible dose, but usually allows postprandial glycosuria, which we have dealt with by appropriate additional injections of regular insulin before breakfast, before breakfast and supper, or before each of the meals. When feasible these multiple injections were replaced by a single dose, before break-

fast, of a suitable mixture of regular and protamine insulins or by NPH insulin.

We employed the above-enumerated principles to guide the readjustment of insulin dosage and type when necessary to secure full diabetic control for each camper. Under the conditions of camp and in the allotted time, this goal was not reached. We realized this aim in only 10 per cent of cases; in 50 per cent we fell short by relatively little, giving a total of 60 per cent with diabetes managed almost to our satisfaction. In 3 per cent we utterly failed.

To secure the above-cited degree of diabetic control, only 12 youngsters or 19 per cent could be treated with a single insulin preparation administered once daily, predominantly NPH insulin; 32 children or 51 per cent required two insulin preparations injected before breakfast each day. The three types of insulin—rapidly-acting regular, NPH or lente insulin with intermediate action, and protamine zinc insulin with prolonged action—were necessary in 17 cases or 27 per cent of the entire group. Insulin administration was given before breakfast only in over 95 per cent of cases; in 4.8 per cent an additional dose of regular insulin was given before supper. In summary, with the insulin products now available juvenile diabetes can be controlled almost entirely by administration before breakfast. In one-fifth of cases we employed one; in one-half, two, and in one-quarter, three preparations. Correlated with this mode of insulin therapy we used measured diets affording a daily range of 1,500 to 3,300 calories, 130 to 280 gm. of carbohydrate, 70 to 130 gm. of protein and 65 to 185 gm. of fat, distributed as a rule in three equal meals, with supplementary feedings as required by unusual exertion or prescribed by particular physicians.

In addition to insulin and diet, the third major problem in dealing with the young diabetic is the recognition and care of insulin hypoglycemia. As a safeguard during the day one or more members of the medical staff participated with each group of campers in the various activities and during the night every three hours a physician with several nurses made rounds through the cabins with flashlights. While the typical symptoms of hypoglycemia such as excess sweating or pallor clearly indicate an insulin reaction, frequently the manifestations in sleep are much more subtle and consist merely of a slight change in usual appearance, pallor around the mouth or across the bridge of the nose, or a deviation from the ordinary position of slumber or manner of breathing. Especially helpful is a prompt squint in response to a strong flashlight beam directed straight at the pupil through the closed eyelid, a maneuver which does not disturb sleep and which with positive response almost certainly excludes severe hypoglycemia. A cardinal rule to follow in checking for insulin reactions by night, is to awaken completely any child who arouses suspicion. During the 1954 season, glucose was administered intravenously to relieve severe insulin reactions on four occasions.

3. *Education*: The youngsters gave no indication that camping pleasures were diminished by the program of diabetic education, which was partly by formal instruction but chiefly by appropriate guidance and direction of daily activities. The camper four times a day tested his urine, using the semiquantitative Clinitest tablets under the supervision of nurses or counselors so that the urinalyses were technically correct. When 2 per cent or heavier glycosuria was found, acetone and diacetic acid tests were made. Soon the camper learned to correlate the result of his urinalysis with his food intake, insulin dose, and activity. He saw that glycosuria could be eliminated by more strict dietary adherence, more vigorous activity or adjustment of insulin dosage.

After the morning urinalysis came insulin administration. Physician, nurse, and counselor were present in each cabin to watch every child closely to check on the accuracy of dosage measurement, the technic of injection and to teach the necessity of rotating sites of administration and of avoiding areas of fibrosis or atrophy. Shortcomings were detected and corrected, so that by the close of the camp session all save the mentally deficient were thoroughly trained in the proper technic of insulin injection.

The cabin nurse and counselor head the dining table for their respective cabin and were trained to teach good food habits. Effort was made to have the children eat what was set before them and they were taught the necessity of correctly substituting for whatever was not consumed. Each child had a copy of his diet and learned to correlate the items with the measured portions from the diet kitchen. The low carbohydrate vegetables were not accurately weighed but served by approximate measure in family style at the table, giving an atmosphere of informality to the meal.

Formal instruction in the various phases of diabetes was scheduled for 30 to 45 minutes each day following the noon meal. Effective use of the Strip Films produced by the United States Public Health Service has been made for several years. One or more aspects were discussed at each period. This method of teaching has proved satisfactory, for in an examination at the close

of camp, the children displayed a well-rounded knowledge of diabetes, its complications and routine management. With tact and good will, it was possible to reconcile divergent views on diabetes, preserve one's principles and practices, and not compromise those of other physicians.

CONCLUSION

The two weeks of camp afford a pleasurable and effective method of correlating play with good diabetic control. During this period, the goal of full control of diabetes (as judged by chemical tests) was attained in only 10 per cent and closely approximated in 50 per cent of the 63 children who attended in 1954. With present-day liberal diets, this degree of diabetic control can be realized as a rule by insulin administration before breakfast alone, employing one insulin preparation in 20 per cent; two in 50 per cent, and three in 25 per cent of cases.

The juvenile diabetic discovers that he is not alone in his need for a regulated diet and injections of insulin. By daily example, he learns to correlate his insulin dose with diet and exercise on the basis of urine tests, blood sugar determinations and hypoglycemic reactions. He carries home the knowledge he can lead a happy, active life and adequately manage his diabetes. Willingness to cooperate cheerfully springs from understanding of the condition. Because camp imparts these things, it is a source of satisfaction to those who conduct it.

SUMMARIO IN INTERLINGUA

Surveliantia del Camping de Diabeticos Juvenil

Le valores recreational, therapeutic, e educative de camping pro diabeticos juvenil es generalmente recognoscite. Le facto que le Statos Unite e Canada offereva in 1954 a lor approximativemente 30.000 diabeticos de etate minor non plus que 25 camps con facilitates special pare indicar que le difficultates involvite in le organisation de un tal interprisa es generalmente considerate como prohibitive. Pro corriger iste prejudicio e pro incoragiar futur emulatores, le autores summarisa lor experientias a Camp Seale Harris in Alabama inter 1948 e 1954.

Le programma de activitates general elaborate pro le campatores diabetic non differeva grandemente del norma usual in altere camps. Le requirimentos special de dieta e surveliantia medical exigeva un personal inusualmente numerose. In 1948 Camp Seale Harris habeva 13 campatores e un personal de 6 personas. In 1954 le duo numeros habeva montate a 65 e 34. Ben que le personal consisteva integremente de empleatos pagate, le budget del camp nunquam excedeva $3500. Le duration del camping esseva restringite a 2 septimanas. Le sito esseva facite disponibile per le Girl Scouts de Mobile al fin de lor proprie saison de camping. Donationes caritabile rendeva possibile que nulle interessato debeva esser rejicite pro rationes financiari.

Durante le camping de 1954 un cautemente elaborate programma de surveliantia medical resultava in complete o quasi-complete controlo de diabete in 60 pro cento del campatores. Le autores conclude super le base de lor experientias que un tal resultato es obtenibile—con pauc exceptiones—per administrationes de insulina solmente ante le prime repasto del die. A Camp Seale Harris in 1954 illes usava un sol preparato de insulina in 20 pro cento del casos, duo preparatos in 50 pro cento, e tres in 25 pro cento.

Le effecto del camping es que le juvene diabetico apprende que ille non es isolate in su requirimentos dietari e medical. Ille porta con se al fin del camping le conviction que ille pote facer se maestro de su diabete e viver un felice e active vita.

Abscess of the Pituitary Gland in a Diabetic Patient

The Houssay Phenomenon in Man

J. H. Brenner, M.B., Ch.B., Cincinnati*

When the pituitary gland is destroyed by any disease process in a diabetic who survives, conditions may develop which are analogous to those in the Houssay animal. Before considering a case of this type, it should be noted that abscess of the pituitary gland is extremely rare. One case of caseous necrosis of the pituitary without evidence of tuberculosis elsewhere in the body, and four cases of syphilis with gummatous destruction of the pituitary gland have been described in the earlier literature, which was reviewed by Plaut.[1] Abscesses of the pituitary gland have been reported, but in these cases the infection has been so rapidly overwhelming that the manifestations of hypopituitarism have not developed or have been entirely obscured.

There are ten recorded cases of the Houssay phenomenon in man.[2, 10] Three patients survived, with a clinical picture of hypopituitarism and amelioration of the diabetic state; seven died. In all the fatal cases there was more or less rapid disappearance of diabetic symptoms and signs, and death was directly associated with severe hypoglycemia. Autopsies were performed in six of the cases, and each revealed necrosis of the pituitary gland. This necrosis was noninfectious and presumably of avascular type, although what stayed the flow of blood through the capillary sinuses of the anterior pituitary is uncertain.

Kraus[11, 12] wrote that whereas necrosis of the pituitary gland is occasionally an incidental finding at autopsy, this condition is more common in the diabetic. However, the distinction between focal necrosis in the diabetic and in the nondiabetic has not yet been demonstrated microscopically. It is probable that most of the anterior pituitary must become necrotic before the patient can present the clinical picture of hypopituitarism.

A case of virtually complete destruction of the pituitary gland by abscess formation in a diabetic is here reported.

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CASE REPORT

A sixty-two-year-old woman was admitted to the Jewish Hospital on June 15, 1953. She had been in good health five months previously, when her husband died. She then became increasingly apathetic toward her daily routine; her appetite was poor, and she lost 40 pounds in five months. This loss had not disturbed her, because she believed that she was too fat and needed to lose weight. During this time she had no other complaint.

For about seven years the patient had known that she was a diabetic. This had been discovered by chance on routine urine examination. She had never had a blood sugar examination, nor received insulin, nor followed any special diet. Her mother had been a diabetic for many years before her death.

During the four weeks prior to admission the patient suffered progressive generalized weakness, swelling of the ankles, and shortness of breath. She had no cough or any other symptoms.

On physical examination the patient appeared to be well developed and well nourished and looked younger than her stated age. There was no evidence of recent loss of weight. She answered questions slowly and intelligibly, but gave the impression that this was an effort. The temperature was 101.2°F., the pulse rate 100, and the blood pressure 135/80. She was rather pale but was neither cyanotic nor dyspneic at rest. There was marked edema of both lower legs, slight edema of the thighs and presacral region, and moderate distention of the neck veins, which disappeared at an elevation of 45 degrees. There was diminished expansion at both lung bases, more marked on the right than on the left. There was dullness to percussion at both bases, more so on the right. The breath sounds were normal, with marked diminution of intensity at the right base. Coarse rales could be heard in both lower zones and in the right mid-zone. The heart was apparently not enlarged; the rhythm was regular and the sounds were normal; there was a short, soft, apical systolic murmur. The optic fundi showed grade 1 arteriosclerotic changes. The liver edge was palpated 6 cm. below the right costal margin and was slightly tender.

A chest X-ray film showed congestive changes at both bases, with possible pneumonitis of the right base. The transverse diameter of the heart was slightly increased, and the right costophrenic angle was obliterated by a small amount of fluid.

The urine contained sugar graded 4 plus, a trace of acetone, and many pus cells.

The impression at this time was that of mild diabetes, with congestive cardiac failure due to arteriosclerotic heart disease, probable superimposed pneumonitis of the right lower lobe, and an asymptomatic urinary tract infection.

Hospital Course

The patient was digitalized and was given 2 cc. of mercuhydrin intramuscularly, 500,000 units of crystalline penicillin every 6 hours, 1 gm. of sulfadiazine every four hours, and 10 units of regular insulin daily.

During the next two days she showed marked improvement. The signs of congestive failure rapidly subsided, as did the temperature. The rales disappeared from both lung fields, although some dullness to percussion persisted at the right base. The liver was no longer tender, but remained palpable. The peripheral edema disappeared. The urine showed only a few pus cells.

The fasting blood sugar was not determined, but as shown in table 1 the patient was excreting a fair amount of sugar in the urine each day.

On the third hospital day, the patient had a mild cough for the first time and produced a small amount of thin, whitish, viscid sputum. On the evening of the next day she had a chill, and the following morning fever still persisted. Thoracentesis in the right costophrenic angle produced only 40 cc. of clear amber fluid. It had a specific gravity of 1.012, contained only a few lymphocytes, and was sterile on culture. Treatment with penicillin and sulfadiazine was stopped, and the patient was given 250 mg. of Terramycin every six hours.

On the sixth day she excreted no sugar in the urine, and no insulin was given after this date. Her intake of a regular soft diet remained adequate. Throughout the afternoon and evening of the seventh day the patient's general condition rapidly deteriorated. She became very lethargic, would take nothing by mouth, and became incontinent of feces and urine. Repeated physical examination failed to reveal any new sign which could account for her rapidly worsening condition. During the seventh day she received 200 gm. of sugar intravenously.

On the morning of the eighth hospital day the patient could not be roused. An emergency blood sugar test gave the value of 11 mg. per 100 cc. (she had no sugar in the urine for the last three days). During the eighth day she received a total of 325 gm. of sugar intravenously, and in the afternoon the urine showed a trace of sugar. Her coma deepened. On the following morning, the blood sugar was 28 mg. per 100 cc. and the patient was still in coma. A spinal tap showed a slightly cloudy fluid with 266 cells per cu. mm., 176 white cells (84 per cent lymphocytes, 16 per cent neutrophils), and 90 red cells. The smear showed occasional gram-negative bacilli, morphologically resembling *Esch. coli*. The fluid was sterile on culture.

The patient died that afternoon. No cultures from the blood or the urine had been made.

Autopsy Report

Autopsy was performed twelve hours after death by Dr. S. Adriano, of the Department of Pathology, Jewish Hospital. The kidneys were slightly larger than usual. The capsules stripped off with ease, revealing several large, coalescent perinephritic abscesses containing creamy yellow pus. Both kidneys had multiple coalescent abscesses, which had destroyed the greater portion of the parenchyma. The calices, pelves, and ureters were not dilated.

In both pleural cavities there was a small amount of clear, amber fluid. Both lung surfaces showed several small nodules below the pleura, which on section appeared to be small abscesses surrounded by fibrous tissue.

The pericardium contained about 25 cc. of slightly turbid fluid. The heart was of normal size; the coronary vessels exhibited well marked calcified atherosclerosis. The pancreas was average in size and shape and felt normal. The adrenal glands appeared normal. The brain and meninges showed no abnormality, but the lateral ventricles contained slightly cloudy fluid. The pituitary fossa was slightly enlarged, and the gland appeared to be completely replaced by an abscess. There was questionable osteomyelitis of the sella turcica. It was the opinion of the pathologist that the pituitary abscess was at least three or four days old.

Microscopic Findings. A section of the sella turcica disclosed areas of fibrosis in the marrow spaces and a number of areas of active acute inflammatory reaction. Sections of the pituitary gland revealed almost complete necrosis of tissue.

TABLE 1

Laboratory data

Hospital day	1st	2d	3d	4th	5th	6th	7th	8th	9th
Sugar excreted in urine in 24 hrs. (gm.)	15.5	14.6	25.2	6.9	14.3	0	0	0	0
Insulin, units	10 Regular	10 NPH	10 NPH	10 NPH	10 NPH	10 NPH	—	—	—
Blood sugar (mg. per 100 cc.)								11 (8 a.m.)	28 (8 a.m.)
White cell count	12,150		17,000		9,500			11,750	
Per cent neutrophils	85		88		88			74	
Maximum temperature	102.4	102.6	100.1	103.2	102.7	99.2	102.8	104.2	104.0

Only a few small areas of recognizable glandular structure could still be seen. In these regions the cellular detail was poorly preserved. In some areas there was considerable cellular infiltration by polymorphonuclear leukocytes and macrophages; in other areas there was complete loss of cell detail with necrosis. Nothing suggestive of infarction was seen. No bacterial masses were recognized.

The kidneys had large areas of abscess formation with considerable cellular infiltrate. The glomeruli varied in appearance; many of them had a crescent formation, and many contained thickened preglomerular capillaries. No scars were seen. Tubules in the intact portions of the kidney contained somewhat swollen and considerably vacuolated lining cells. Sections of the pancreas and adrenal glands disclosed no abnormality. Sections of the lung revealed small areas of abscess formation with many polymorphonuclear leukocytes as well as large macrophages.

Pus from both the pituitary fossa and the kidney was sterile on culture. A smear of the renal pus showed gram-negative bacilli, morphologically resembling *Esch. coli*. Unfortunately, a smear of pituitary pus was not made.

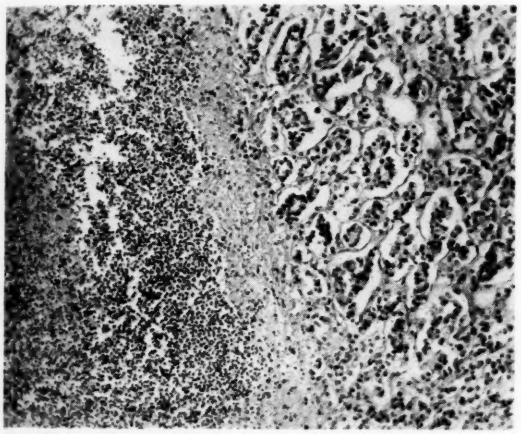

FIG. 1. Anterior pituitary gland (X 160). On the right can be seen recognizable pituitary tissue, poor in cellular detail; on the left, necrotic tissue with heavy cellular infiltration.

COMMENT

This case illustrates the remarkable silence of a severe renal infection which was underestimated because of the concurrent pulmonary findings and the initial response to antibiotic therapy. The abscess in the pituitary fossa presumably developed four or five days after admission. The hypoglycemia developed during the seventh night. (Intravenous infusion of fluids had been stopped at 7:30 p.m.) Such a short period of fasting has led to hypoglycemia in many reported cases of pituitary or adrenal insufficiency. In this case, fever may have masked the metabolic response to destruction of the pituitary at an earlier date. However, it is most unusual to observe hypoglycemia after a relatively short fast in a patient whose fever has persisted. One can only interpret this as due to a severe destruction of the anterior pituitary, with inadequate function of the cellular remnants. Death was probably caused directly by prolonged hypoglycemia.

SUMMARY

A woman who had had diabetes for seven years was admitted to hospital suffering from septicemia which terminated fatally. There were widespread metastatic abscesses; the offending organism was probably *Esch. coli*. At first she required a small amount of insulin, but during the last few days of life she exhibited the Houssay phenomenon, in that she had a tendency to spontaneous hypoglycemia. Autopsy revealed virtually complete destruction of the pituitary gland by an abscess.

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SUMMARIO IN INTERLINGUA

Abscesso del Glandula Pituitari in un Patiente Diabetic: Le Phenomeno de Houssay in Humanos

Un femina, qui habeva habite diabete durante septe annos, esseva admittite al hospital con septicemia que se terminava in le morte del patiente. Esseva constatate extense abscessos metastatic. Le organismo responsabile esseva probabilemente *Escherichia coli.* Initialmente le patiente requireva un parva quantitate de insulina, sed durante le ultime dies de su vita illa exhibiva le phenomeno de Houssay manifeste in un spontanee tendentia hypoglycemic. Al autopsia le quasi complete destruction del glandula pituitari per un abscesso esseva constatate.

Clinical Importance of Protein Metabolism

The dormant state following the first spurt of work on "toxic destruction of proteins" in clinical conditions may have been partly due to the fact that there was little therapeutic application of what was learned from these previous studies. The revival of interest in clinical proteinology may be attributed to the dramatic results of the application of high protein intake in surgical conditions. In relatively rapid succession came the introduction of the intravenous use of protein hydrolysates by Shohl *et al,* subsequently carried forward by Elman *et al,* into surgical conditions, and the series of reports by Co Tui and his group on protein loss and the effect of hyperproteinization in decubitus ulcers, in gastric surgery, and in burns.

Of interest to clinical proteinology are the findings of the Co Tui group, subsequently supported by the reports of other workers, that: (1) proteins are essential to the maintenance of tissue integrity; (2) the level of protein intake for the hypoproteinic patient may have to be as high as 250-500 gm. daily—that is, the optimum level for replenishment approximates or even exceeds that for optimum growth; (3) the hypoproteinic subject is able to deposit nitrogen far in excess of what contemporary writers have thought possible; (4) the large deposition of nitrogen is associated with acceleration of rehabilitation and convalescence; (5) the catabolic or antianabolic period following injury can be eliminated by increasing the level of intake.

These points furnish the major scaffolding on which clinical proteinology is being built.

Protein Deficiency in Internal Medicine of Pediatrics

Although the work on "toxic destruction of proteins" was done on medical conditions, and although Albright's monumental work on Cushing's disease and Farr's study of nephrosis gave medical proteinology a good start, it cannot yet be said that the protein factor in general medical conditions is fully appreciated.

Many ulcer patients suffer from hypoproteinia, although this deficiency is rarely reflected in the plasma protein level. Heretofore, this hypoproteinia has been attributed to a reduction in intake resulting from distress, or to the neglect of the nutritional factor in the preoccupation with the antacid factor. However, the observations of Gray on chronic stress in peptic ulcer indicate that the oversecretion of protein catabolic agents in "chronic stress" may play a role in causing hypoproteinia in this disease.

Hypoproteinia retards wound healing, and it is in the correction of this deficiency by inducing acceleration of wound healing that protein hydrolysate plays its nutritional role.

The results reported by Boines on the application of hyperproteinization in poliomyelitis, and by Ravdin, *et al,* Vars and Gurd, and Morrison, in liver disease, the work on the effect of adequate protein intake on corticotropin (ACTH) production and the role in turn of corticotropin on the renal excretion of a pressor substance, linking protein metabolism through endocrinology with hypertension, augur a brilliant future in this field.

Although earlier work centered mostly on growth, the effects of disease on protein nutriture and vice versa have not received attention until recently. Yet it was actually in pediatrics that protein hydrolysate was first used. Recently Miranda and Lynch have called attention to "hypoproteinosis" in children and to the necessity for its correction by an adequate diet.

From "Review: The Fundamentals of Clinical Proteinology" by Co Tui, M.D., in *The Journal of Clinical Nutrition,* March-April, 1953.

Recent Statistics on Diabetes

The death rate from diabetes last year was appreciably less than in 1953. Despite the increase in the country's population there was apparently a small decrease in the absolute number of deaths from the disease. Provisional data based upon a 10 per cent sample of death certificates collected by the National Office of Vital Statistics indicate that the number of deaths from the disease in 1954 was slightly under 25,000. The estimated death rate was 15.4 per 100,000 or nearly 4 per cent less than in 1953. In the urban wage-earning population, represented by Industrial policy-holders of the Metropolitan Life Insurance Company, the decline in the diabetes death rate between 1953 and 1954 was 4½ per cent, or slightly larger than in the general population.

The cities in the United States and Canada and the two states for which data are obtained regularly experienced a lower death rate in 1954 than in 1953, with but a single exception, namely, Maryland, where the rates for the two years were identical (table 1). The reduction in the diabetes death rate reflects a generally satisfactory level of health conditions during the year. Not only did the general death rate decline, but last year's death rate was the lowest ever recorded, according to provisional figures, for the country as a whole, for the urban population represented by the Metropolitan's experience, and for New York City.

England and Wales also recorded a reduction in the diabetes death rate last year. The data for London Administrative County showed a decline of approximately 12 per cent in 1954 as compared with 1953. For the country as a whole the rate for the first nine months was 8 per cent less than in the corresponding period of 1953. The decline was somewhat greater among females than males, 9 per cent and 6 per cent respectively.

Regional data for 1954, based on the 10 per cent sample of death certificates, showed that the 1954 death rate from diabetes was less than that of 1953 in the North and the Mountain Area. Provisional rates for the two years were identical in the South Atlantic States, and for the West South Central Area the 1954 rate was higher by a small margin. In the two remaining areas, East South Central and Pacific Coast, the rates were up rather sharply last year from 1953. In some of these areas the number of deaths in the sample is small and, therefore, may not give a true indication of the trend (table 2).

The final figures on diabetes mortality, by region and state, are now available for 1952. These are shown in table 3 along with the corresponding figures for 1951 and 1950. In 1952, the rates remained highest in the East and in the Middle West. In fact all the states along the Atlantic Seaboard from New Hampshire to Maryland and west to the Mississippi experienced rates higher than the national average. Generally speaking, the rates were below the average for the country in the states in the South and elsewhere with large rural or nonwhite populations. The death rate in Rhode Island was still the highest in the country despite a fall of about one-fifth in the rate for the state from that recorded in 1950. New Mexico and Arizona had the lowest death rates from diabetes in the nation in 1952.

The level of mortality ascribed to diabetes underwent a sharp reduction with the inauguration of the Sixth Revision of the International List of the Causes of Death, reflecting mainly the new procedure of the cause of death to be tabulated that was an integral part of the revision.† Generally, the use of the new List began in 1949, but in some places not until 1950. Now that the mortality data on the new basis are available for five to six years, it will be of interest to review the facts as they relate to diabetes. They are presented for three separate series: the country as a whole, New York City, and the experience of the Metropolitan Life Insurance Company on the urban wage-earning population (table 4). For the whole country, and for New York City, the death rate from diabetes in 1954 was the lowest of any year since 1949, and in the Metropolitan's experience since 1950, next to the lowest. The estimated rate for the United States in 1954 was 9 per cent under that of 1949. In comparison the death rate for *all causes combined* in 1954 was down 5 per cent from 1949. In New York City during the same interval the death rate from

*Submitted by the Committee on Statistics, Herbert H. Marks, Chairman. The Committee welcomes suggestions or actual material suitable for this section in future issues, from Association members and other readers of the *Journal*.

†The material which follows is based upon the talk by Herbert H. Marks at the *Symposium on Diabetes* of the Section on Medicine of the New York Academy of Medicine, Jan. 18, 1955.

TABLE 1

Recent data on diabetes mortality
Deaths and death rates—1954 and 1953

Area	Death Rates per 100,000		Number of deaths	
	1954	1953	1954	1953
United States (10 per cent sample)	15.4	16.0	2,482	2,539
Metropolitan Life Ins. Co. Industrial Policyholders	14.9	15.6	2,726	2,884
New York State	19.9	20.4	3,121	3,158
New York City	19.3	20.4	1,568	1,654
Maryland	16.8	16.8	428	421
Baltimore, Resident	18.6	19.5	180	188
Boston, Resident	19.0	21.2	154	172
Philadelphia	26.8	29.4	576	627
Toronto	15.8	18.0	108	120
Montreal, Resident	16.6	19.7	177	207
London (Administrative County)	6.8	7.7	226	257
	Jan.-Sept.		Jan.-Sept.	
	1954	1953	1954	1953
England and Wales				
Total	6.9	7.5	2,287	2,486
Males	5.0	5.3	797	848
Females	8.7	9.6	1,490	1,638

Note: Rates for the states and cities are based upon local estimates of population. United States data based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in *Current Mortality Analysis*, a monthly report of the National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 2

Number of deaths and death rates from diabetes in geographic division; United States reporting area for the 10 per cent sample; 1954, 1953 and 1952

Geographic Division	Death Rates per 100,000*			Number of deaths*		
	1954	1953	1952	1954	1953	1952
U.S. reporting area	15.4	16.0	16.2	2,482	2,539	2,525
New England	17.3	18.4	20.2	170	178	191
Middle Atlantic	21.2	22.6	22.2	668	702	682
East North Central	18.3	20.4	19.0	595	651	602
West North Central	15.1	17.2	18.1	220	247	256
South Atlantic	12.5	12.5	12.3	289	281	273
East South Central	10.8	8.8	10.5	126	102	120
West South Central	10.9	10.6	10.5	169	162	158
Mountain	7.6	9.9	14.9	44	55	81
Pacific	12.0	9.9	10.4	201	161	162

*Excludes armed forces overseas.

Note: These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the *Current Mortality Analysis*.

Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

diabetes declined 5 per cent and that from all causes 2 per cent. In the Metropolitan's experience since 1950, the death rate from diabetes decreased about 4 per cent compared with a 2½ per cent fall in the death rate from all causes.

Accordingly, there has been a small but fairly persistent decline in the proportion of all deaths ascribed to diabetes. In the United States deaths ascribed to diabetes in 1949 constituted 17.4 per thousand of all deaths as compared with 16.8 in 1954. In New York City this proportion declined from 20.4 in 1949 to 19.8 in 1954. This indicates an increasing propensity on the part of physicians to ascribe deaths of diabetics to complications or to concurrent diseases.

Information on the relative frequency with which diabetes is recorded on death certificates as a primary and as a contributory cause of death is available from special analysis of New York City's death certificates for January 1954,* and from a study of death claims paid by the Metropolitan Life Insurance Company (all departments) during the last two weeks of 1954. The New York City study showed that 102 deaths were ascribed to diabetes as the underlying cause as compared with 176 deaths in which it was reported as the contributory or associated cause. In other words, of the 278 known deaths among diabetics, only 37 per cent were ascribed to the disease. This ratio is probably much lower than is generally recorded elsewhere in the country. In the Metropolitan's study, diabetes was given as the underlying cause in 170 or 60 per cent of 285 deaths in which diabetes was mentioned in the claim records. The figures cited actually understate both the total mortality of diabetics and the frequency of the disease as an associated or contributory cause, because the number of diabetics dying as a result of violence (accidents, homicide and suicide) and of some diseases, notably maligant conditions, is under-reported.

Special analysis of the causes of death in diabetics in the general population also reveal important facts. The significance of these findings is brought out by comparing them with the experience of the Joslin Clinic on diabetics whose deaths occurred and were reported during 1954. Two major conclusions may be drawn from the figures: (1) diabetic coma and diabetic gangrene are still relatively frequent causes of death in the general diabetic population, and (2) the differing points of view of physicians with regard to the relationship between

*Unpublished data furnished by Carl L. Erhardt, Director, Bureau of Records and Statistics, and Louis Weiner, Chief, Statistical Division, New York City Department of Health.

TABLE 3

Death rates per 100,000 from diabetes in the United States by geographic region and state,* 1952, 1951, and 1950

Region and State	1952	1951	1950	Region and State	1952	1951	1950
United States	16.4	16.3	16.2				
New England	20.7	22.8	21.0	South Atlantic (con't.)			
Maine	15.9	19.7	16.9	West Virginia	14.4	10.7	12.2
New Hampshire	21.8	21.9	20.1	North Carolina	9.3	9.3	9.8
Vermont	19.6	16.6	15.9	South Carolina	11.8	11.9	13.4
Massachusetts	21.5	24.2	20.5	Georgia	12.1	12.5	12.0
Rhode Island	29.0	30.7	35.9	Florida	13.1	12.2	12.7
Connecticut	17.7	19.1	19.3				
				East South Central	11.0	11.0	10.2
Middle Atlantic	21.6	20.9	20.5	Kentucky	13.8	12.7	11.9
New York	20.6	19.6	19.0	Tennessee	9.1	9.1	9.5
New Jersey	21.4	21.7	19.7	Alabama	10.2	10.7	8.9
Pennsylvania	23.3	22.4	23.0	Mississippi	11.4	12.2	10.8
East North Central	19.8	20.2	20.6	West South Central	11.5	11.7	11.6
Ohio	24.0	23.9	22.5	Arkansas	8.9	9.8	9.4
Indiana	18.1	17.2	17.9	Louisiana	14.5	14.4	12.5
Illinois	17.1	18.3	19.5	Oklahoma	13.1	12.9	13.4
Michigan	19.8	21.1	21.9	Texas	10.6	11.0	11.3
Wisconsin	19.0	18.2	19.5				
				Mountain	11.7	11.3	10.3
West North Central	17.5	17.0	17.9	Montana	16.1	13.4	11.5
Minnesota	16.6	16.5	17.0	Idaho	13.4	14.9	14.1
Iowa	16.9	17.4	17.4	Wyoming	11.8	16.1	11.4
Missouri	17.7	17.4	18.5	Colorado	11.0	10.8	10.9
North Dakota	16.9	19.1	17.6	New Mexico	7.3	7.8	5.6
South Dakota	18.0	14.7	17.8	Arizona	10.6	7.8	8.4
Nebraska	19.7	18.5	19.5	Utah	14.7	12.2	11.3
Kansas	17.6	15.6	17.9	Nevada	7.6	13.5	10.6
South Atlantic	12.5	12.0	12.6	Pacific	11.0	11.1	10.0
Delaware	23.0	21.2	27.0	Washington	15.1	16.0	14.2
Maryland	17.9	17.9	17.0	Oregon	11.6	11.7	11.2
District of Columbia	13.9	12.7	15.1	California	10.0	9.9	8.8
Virginia	10.5	10.1	11.0				

* By place of residence. Excludes Armed Forces Overseas.
Source: National Office of Vital Statistics of the U. S. Public Health Service. Special Reports –National Summaries.

TABLE 4

Death rates per 100,000 in specified populations from all causes and from diabetes
Based upon Sixth Revision of International List, 1949-1954

	United States		New York City		Metropolitan Life Insurance Company	
Year	All Causes	Diabetes	All Causes	Diabetes	All Causes**	Diabetes
1949	971.0	16.9	1,000	20.4	—	—
1950	963.8	16.2	1,001	20.0	635.8	15.5
1951	966.3	16.3	984	19.4	645.5	15.2
1952	961.0	16.4	1,003	20.4	651.3	14.4
1953	960.2	16.1*	1,012	20.4	646.1	15.6
1954	920.9*	15.5*	980*	19.3*	620.1	14.9

*Estimated
**Excluding war deaths

diabetes and other morbid conditions existing at time of death greatly affect the reported mortality from the disease. The first conclusion is borne out by a comparison of the causes of death reported for deceased diabetic policyholders in the Metropolitan's experience in December 1954 with the corresponding experience of the Joslin Clinic in 1954 (table 5). Some differences arise out of the fact that the Joslin Clinic experience is based upon a follow-up of known diabetics, whereas the insurance material, based on currently reported claims, is subject to the limitation mentioned earlier, namely, the presence of diabetes is often unreported on death certificates. Nevertheless, it is notable that diabetic coma was present in nearly 5 per cent of the diabetics in the Metropolitan's experience as compared with less than 1 per cent in the Joslin Clinic patients. For diabetic gangrene, the proportions were 6 per cent and 3 per cent respectively. Deaths from diabetic nephropathy were relatively fewer in the insured group than in the Joslin Clinic experience. This probably reflects differences in the reporting of the condition, and perhaps also the higher proportion of cases of longer duration in the Joslin Clinic.

Among diabetics in the Metropolitan's study, as well as among those of the Joslin Clinic, arteriosclerosis predominated as the cause of death. Heart disease accounted

TABLE 5

Per cent of deaths ascribed to specified causes among diabetics. By sex.
Experience of Metropolitan Life Insurance Company policyholders* and of Joslin Clinic compared†

Cause of Death	Metropolitan Life Insurance Company			Joslin Clinic		
	Both Sexes	Males	Females	Both Sexes	Males	Females
	Per cent of all causes					
All Causes, excluding unknown	100.0	100.0	100.0	100.0	100.0	100.0
Diabetic coma (primary)	4.8	6.1	4.1	.7	.8	.7
Arteriosclerotic	83.0	82.8	83.1	72.0	71.4	72.6
Cardiac	52.4	56.6	50.0	44.0	48.1	40.0
Coronary and angina	28.4	39.4	22.1	35.8	39.8	31.9
Renal	6.6	7.1	6.4	9.7	11.3	8.1
Diabetic nephropathy	2.6	5.1	1.2	5.6	4.5	6.7
Cerebral	14.8	7.1	19.2	14.6	9.8	19.3
Gangrene	5.9	7.1	5.2	2.6	1.5	3.7
Site unassigned	3.3	5.1	2.3	1.1	.8	1.5
Cancer	5.9	5.1	6.4	11.6	9.8	13.3
Violence	.7	—	1.2	4.9	6.0	3.7
Other diseases	5.5	6.1	5.2	10.8	12.0	9.6
Total number of deaths	285	104	181	268	133	135
Cause unknown	14	5	9	—	—	—

*All Departments. Deaths during last 2 weeks of 1954.
†Deaths occurring during 1954, reported to 12/21/54.

TABLE 6

Per cent of deaths from specified causes among diabetics. By sex.
Deaths ascribed to diabetes and to other causes compared
Experience of Metropolitan Life Insurance Company policyholders*

Cause of Death	Both Sexes		Males		Females	
	Death ascribed to					
	Diabetes	Other Causes	Diabetes	Other Causes	Diabetes	Other Causes
	Per cent of all causes					
All Causes, excluding unknown	100.0	100.0	100.0	100.0	100.0	100.0
Diabetic coma (primary)	8.3	—	10.7	—	7.0	—
Arteriosclerotic	87.8	76.5	83.9	81.4	90.0	73.6
Cardiac	47.4	59.1	50.0	65.1	46.0	55.6
Coronary and angina	24.4	33.9	35.7	44.2	18.0	27.8
Renal	10.3	1.7	12.5	—	9.0	2.8
Diabetic nephropathy	4.5	—	8.9	—	2.0	—
Cerebral	18.6	9.6	7.1	7.0	25.0	11.1
Gangrene	7.7	3.5	8.9	4.7	7.0	2.8
Site unassigned	3.8	2.6	5.4	4.7	3.0	1.4
Cancer	.6	13.0	1.8	9.3	—	15.3
Violence	—	1.7	—	—	—	2.8
Other diseases	3.2	8.7	3.6	9.3	3.0	8.3
Total number of deaths	170	115	61	43	109	72
Cause unknown	14	—	5	—	9	—

*All Departments. Deaths during last 2 weeks of 1954.

for about three-fifths of the arteriosclerotic deaths in both series. Cerebral accidents were next in frequency. They accounted for about one-sixth of the arteriosclerotic deaths in the Metropolitan's experience, and for one-fifth in that of the Joslin Clinic. The predominance of arteriosclerotic conditions as causes of death was found in all age groups in both experiences.

According to New York City data for 1953, 7.7 per cent of the deaths ascribed to diabetes were reported as due to diabetic coma and 13.2 per cent to diabetic

gangrene. On the basis of the estimated total number of deaths in which diabetes was mentioned in the death certificate, these proportions were approximately 3 per cent and 5 per cent respectively. All these figures are well above those reported for the Joslin Clinic.

Consideration is next given to an analysis of the causes of death among diabetics, separately for those cases ascribed to the disease and those not so classified (table 6). This comparison was based upon the Metropolitan's experience in December 1954. Of the deaths ascribed to diabetes and for which details were given, diabetic coma and diabetic gangrene each accounted for about 8 per cent, and diabetic nephropathy for an additional 4 per cent. Thus, only one-fifth of these deaths were ascribed to specific complications of diabetes. Moreover, even if we assume that all the renal deaths and all those lacking detailed information on cause of death were due to complications of diabetes, this total would account for less than one-third of all the deaths ascribed to it. Arteriosclerotic complications accounted for the great majority of deaths ascribed to diabetes, as well as for deaths of diabetics ascribed to other causes.

Similar results are found in analysis of the facts on the cases included in the New York study previously cited. The data are not directly comparable because every condition reported on the certificate was tabulated in this study. Nevertheless, arteriosclerotic heart disease alone was reported in about one-half of the deaths of diabetics ascribed to diabetes and of those ascribed to other causes (table 7).

TABLE 7

Selected causes of death (1) associated with diabetes as the underlying cause and (2) underlying causes with which diabetes is associated or contributory
New York City, January 1954

Cause of Death	Total	Number of Deaths	
		Diabetes primary	Diabetes contributory
Total from or with diabetes	278	102	176
Arteriosclerosis, total	—	—	123
Central nervous system	36	18	18
Arteriosclerotic heart disease	139	57	82
Other heart disease	7	6	1
Hypertensive heart	29	16	13
Hypertension	9	5	4
Other circulatory	37	33	4
Nephritis and nephrosis	4	3	1
Cancer	23	—	23
Pneumonia	13	4	9

The facts cited indicated that reported deaths from diabetes in recent years are an inadequate measure of the magnitude of the mortality from the disease and may not even be too reliable a guide of the trend of its mortality. Certainly, they are of little value as a measure of the prevalence of diabetes today. Nevertheless, the complete reporting on death certificates of the details of causes of death of diabetics is most desirable. Vital statistics offices should be encouraged to tabulate and analyze the material because the information on mortality due to preventable diabetic complications can be used to stimulate improvement in the treatment of diabetics by physicians in the community, and to bring home to the diabetics the cogent reasons for following closely the rules of care prescribed by their physicians.

ABSTRACTS

Aarseth, S. (*Oslo, Norway*): DIABETES MELLITUS, SURGERY AND ANESTHESIA. Tidsskr. norske laegefor. 74: 449-58, July 1, 1954. (Abstr. in J.A.M.A. *156*:1206, Nov. 20, 1954).

The author advises local anesthesia whenever possible, except that for amputations spinal anesthesia is recommended. In cases with marked infection, necrosis, and poor general condition, freezing has been employed successfully. The duration and depth of the narcosis must be reduced to the necessary minimum. Induction of anesthesia with nitrous oxide and oxygen and continuation with ether are advised for long operations. Premedication with morphine and barbiturates tends to cause anoxia. Chloroform and ethyl chloride are contraindicated. With hepatic affection, which the author considers not uncommon in diabetics, he also advises against the use of tribromoethanol (Avertin) and hexobarbital (Evipal), and corresponding barbituric preparations.

Abbott, William E.; Jefferies, William McK.; Levey, Stanley; Krieger, Harvey (*Western Reserve Univ. Sch. of Med. and Univ. Hosps., Cleveland, Ohio*): TOTAL BILATERAL ADRENALECTOMY FOR ADRENAL CORTICAL HYPERFUNCTION. J.A.M.A. *156*:1168-71, Nov. 20, 1954.

In a patient with long-standing adrenal cortical hyperfunction due to adrenal hyperplasia, total bilateral adrenalectomy has been followed by dramatic improvement in obesity, hirsutism, amenorrhea, diabetes, hypertension, and an associated psychosis during the 23-month period when the patient was followed postoperatively. Replacement therapy with cortisone and desoxycorticosterone acetate has maintained a satisfactory clinical status. A subsequent operation for removal of a cyst from the breast was well tolerated, after an increase in cortisone dosage.

Adams, Theodore W. (*Portland, Ore.*): DIABETES AND PREGNANCY. Obst. & Gynec. 5:160-64, February 1955.

The problems of management of pregnancy in diabetes are discussed. Teamwork between the internists, obstetrician, and pediatrician is essential. The author advises delivery between the 36th and 38th weeks. Cesarean section may be the procedure of choice. The radiological appearance of ossification in the distal femoral epiphysis may aid in determining intra-uterine fetal age.

Annotations (*Lancet, 7 Adam St., Adelphi, London, England*): TUBERCULOSIS AND DIABETES. Lancet *1*: 1058-59, May 24, 1952.

Prevalent viewpoints concerning the association of tuberculosis with diabetes, and comments on recent studies of this problem are presented.

Auld, W. H. R. (*Dept. of Clin. Chem., Aberdeen Univ., Aberdeen, Scotland*): THE HEXOKINASE ACTIVITY OF SKELETAL MUSCLE IN DIABETES MELLITUS. Clin. Sc. *13*:357-64, August 1954.

The hexokinase activity of freshly prepared homogenates of muscle from normal and diabetic human subjects was studied. There was no significant difference in hexokinase activity between the two groups. The addition of insulin in vitro did not alter the rate of hexokinase reaction. No labile inhibitor of hexokinase, as described by Cori and his associates, was encountered.

Avant, J. A., Jr. (*Baton Rouge, La.*): DIABETES IN CHILDHOOD. New Orleans M. & S. J. *104*:662-65, October 1952.

In view of our inadequate knowledge of the subject, the best that can be done is very careful observation of the newborn and a state of readiness to meet any difficulty which might arise. All deliveries should take place within a hospital; oxygen should be available; and tracheal suction should be resorted to if excessive mucus tends to occlude the airway. Glucose solution is frequently used if hypoglycemia is suspected.

Baker, D. G.; and Sellers, E. A. (*Dept. of Physiol., Univ. of Toronto, Toronto, Ontario, Canada*): CARBOHYDRATE METABOLISM IN THE RAT EXPOSED TO A LOW ENVIRONMENTAL TEMPERATURE. Am. J. Physiol. *174*: 459-61, September 1953.

The glycogen content of the heart, liver, diaphragm, and of fat from perirenal and interscapular regions of the rat acclimatized to cold (1-3°C.) is less than that found in the comparable animal kept at room temperature. The glycogen content of the skeletal muscles, and the blood sugar levels of the two groups are not significantly different.

Cold-acclimatized rats show a greater fall in blood sugar after insulin than animals kept at room temperature.

These results are believed to be due to the elevated metabolic rate of the cold-acclimatized animals, with an associated increased utilization of carbohydrate.

Best, Charles H. (*Dept. of Physiol., Univ. of Toronto Med. Sch., Toronto, Canada*): ASPECTS OF THE ACTION OF INSULIN. Ann. Int. Med. *39*:433-43, September 1953.

The author reviews the highlights of many aspects of the action of insulin, and discusses some of the fascinating facets of this problem yet to be investigated.

Burnstein, Norman (*Jackson, Miss.*): RECENT ADVANCES IN DIABETES MELLITUS. Mississippi Doctor *32*: 256-59, February 1955.

A summary of the highlights of recent clinical knowledge, and experimental developments.

Cinotti, A. A.; and Jacobson, Jerry Hart (*Jersey City, N. J.*): COMPLICATIONS FOLLOWING CATARACT EXTRACTIONS. Am. J. Ophth. *36*:929-36, July 1953.

In a study of 1,001 cataract extractions, it was noted that operations were performed on 99 eyes of diabetics. There was a relatively higher frequency of secondary glaucoma in diabetics than in nondiabetics. The incidence of hemorrhage into the anterior chamber and secondary iridocyclitis was also higher in extracapsular extractions among diabetics. Diabetic retinopathy was severe enough in 18 of these cases to prevent good visual results.

Clarke, Norman E.; Clarke, Charles N.; and Mosher, Robert E. (*Dept. of Res., Providence Hosp., Detroit, Mich.*): THE IN VIVO DISSOLUTION OF METASTATIC CALCIUM. AN APPROACH TO ATHEROSCLEROSIS. Am. J. M. Sc. *229*:142-49, February 1955.

The authors report the synthetic chelating compound EDTA (ethylene diaminetetraacetic acid) is a reasonably safe therapeutic agent for intravenous administration in 5 to 10 gm. doses in 500 to 1,000 cc. of normal saline solution or 5 per cent glucose in distilled water to human subjects and for up to 100 administrations. Skin rashes developed in 5 of 22 patients.

EDTA will remove metastatic calcium from the human body, at least from the parenchyma of the human kidney, without production of hypocalcemia or bone demineralization. After EDTA therapy, reliable estimation of the serum calcium by the oxalate precipitation method requires preliminary destruction of the EDTA (as by wet-ashing with nitric-perchloric acids).

Since there may be an interrelationship between calcium, cholesterol or lipoproteins and atheromatous changes in arterial walls, the authors propose the study of EDTA as a therapeutic agent in atherosclerosis.

Clifton, E. E. (*Dept. of Surg., Cornell Univ. Med. Coll., and Dept. of Clin. Research, Sloan-Kettering Inst., New York, N. Y.*): THE PRESENT STATUS OF THERAPEUTIC USE OF ENZYMES. Am. J. M. Sc. *228*:568-80, November 1954.

In infections of mucosa-lined structures, such as the nose and sinuses, increased penetration and absorption of antibiotics has followed the use of hyaluronidase. It has also been used in lung infections both in suppurative disease with antibiotics for treatment and to enhance the spread of antibiotic in tuberculosis.

Many other suggested uses of these enzymes may prove to be satisfactory, and new enzymes now in process of development may be found very useful especially in treatment of burns (collagenases) and vascular thromboses (plasmin).

Cullimore, Owen S.; Bradshaw, Phoebe J.; Blatherwick, N. R.; and Beach, Eliot F. (*Biochemical Lab. of Metropolitan Life Insurance Company, New York, N. Y.*): LIVER AND MUSCLE GLYCOGEN AS INFLUENCED BY ALLOXAN. Am. J. Physiol. *174*:357-64, September 1953.

A study has been made of liver and muscle glycogen storage in albino rats during alloxan diabetogenesis and under conditions of feeding and fasting in established

alloxan diabetes. In control animals, realimentation after prolonged fasting results in a rebound of liver glycogen to quantities well above normal levels. During alloxan diabetogenesis, the liver glycogen tends to move contrary to the direction of blood sugar changes. In the triphasic response, liver glycogen is low during the hyperglycemic phases and becomes high in the hypoglycemic phase. Established alloxan diabetics, when fed, have normal muscle glycogen but are lower than normal rats in liver glycogen. When fasted, alloxan diabetics show great diversity in blood glucose having hyperglycemia, normal blood sugar levels or hypoglycemia. Most diabetics with fasting hyperglycemia have greater-than-normal liver glycogen as do many with blood sugar in the normal fasting range. Those with fasting hypoglycemia have low liver glycogen. On fasting, many alloxan diabetics develop low muscle glycogen, the animals with fasting hypoglycemia being particularly outstanding in this regard. However, low-fasting muscle glycogen is not confined exclusively to the hypoglycemic group. No evident correlations of glycogen levels in liver and muscle or fasting blood sugar level with ketonuria were found.

Delalla, Oliver F.; Elliott, Harold A.; and Gofman, John W. (*Donner Lab., Div. of Med. Physics, Dept. of Physics and Radiation Lab., Univ. of California, Berkeley, Calif.*): ULTRACENTRIFUGAL STUDIES OF HIGH DENSITY SERUM LIPOPROTEINS IN CLINICALLY HEALTHY ADULTS. Am. J. Physiol. *179*:333-37, November 1954.

Measurements of three high density lipoproteins in the serum of 566 clinically healthy adults have been made. Analysis of the age and sex trends in mean values for the age span 18-69 years is presented. Possible interrelationships in the serum levels of the three high density lipoproteins were evaluated.

Editorial (*3640 University St., Montreal, Canada*): HYPERINSULINISM AND ISLET-CELL ADENOMA. Canad. M. A. J. *72*:39, Jan. 1, 1955.

Symptoms, signs, and diagnostic features of islet-cell adenoma are briefly discussed. Fasting the patient for 12 to 24 hours is considered more helpful in diagnosis than glucose tolerance tests.

Editorials: (*none given*): THE WILMER MEETING. Am. J. Ophth. *36*:993-96, July 1953.

Friedenwald presented evidence that diabetic retinopathy is influenced by adrenal function. Oxysteroid and cortisonelike substances are put out in excess in diabetics with retinopathy. Lesions simulating those found in Kimmelsteil-Wilson disease were produced in 33 per cent of the rabbits to which cortisone alone was given, in 75 per cent of alloxan-diabetic rabbits given cortisone, and in 100 per cent of cortisone-treated alloxan-diabetic rabbits with vitamin B_{12} deficiency. Pantothenic acid and related vitamins improved the adrenal function in diabetics as judged by the greater eosinophilic response to corticotropin.

Diabetics without retinopathy appear to have a tendency to B_{12} deficiency. Diabetics with retinopathy show what seems to be a contradictory increase in excretion of B_{12}, but this is presumably due to excessive functioning of the adrenals in the diabetic, mobilizing all available vitamin B_{12}, thereby masking a relative deficiency of this substance.

Testosterone dampens pituitary and adrenal function, and therefore lessens the excretion of vitamin B_{12} and in this way may help a diabetic retinopathy. Presumably B_{12} deficiency and increased adrenal function increases diabetic retinopathy. In correcting this, one would recommend use of B_{12}, but clinical experience with this treatment to date has been discouraging.

Elwyn, Herman (*New York, N. Y.*): DIABETIC RETINOPATHY. Pennsylvania M. J. *58*:218-20, February 1955.

The incidence of diabetic retinopathy varies with the duration of the diabetes and in a series of patients who have had the disease for over 20 years has been reported as high as 83 per cent. The fundamental cause of diabetic retinopathy is still to be elucidated. The author believes that the hemorrhages and exudates may appear, disappear, and recur in spite of all treatment of the diabetes, but he urges maintenance of an approximately normal blood sugar level by proper regulation of the diet and by means of insulin.

Engel, Frank L.; Hewson, Kathleen; and Cole, B. Theodore (*Depts. of Med. and Physiol., Duke Univ., Durham, N. C.*): CARBOHYDRATE AND KETONE BODY METABOLISM IN THE SODIUM FLUOROACETATE-POISONED

RAT. 'SFA DIABETES'. Am. J. Physiol. *179*:325-32, November 1954.

The effects of intraperitoneal injection of sodium fluoroacetate (SFA) on the blood sugar and ketone levels of 24-hour fasted rats have been studied, because of the known action of SFA establishing a block in the tricarboxylic acid cycle. SFA poisoning was associated with an immediate but irregular increase in blood sugar and ketones and a consistently marked hyperglycemia and hyperketonemia 24 hours after poisoning. SFA poisoning prolonged the duration and degree of ketonemia following an intravenous infusion of sodium octanoate but had no effect on the ketonemia after administration of a fat emulsion by mouth or vein. The enhanced ketonemia in the SFA-treated rat during and after octanoate infusion was interpreted as indicating both increased production and decreased utilization of ketone bodies.

Glycerol monoacetate and glycerol were highly effective in decreasing ketosis immediately and 24 hours later in SFA-poisoned rats and were more effective than glucose. All increased blood sugar levels significantly. Cortisone acetate treatment markedly suppressed ketosis but had no influence on the blood sugar levels of SFA-poisoned rats. The hyperglycemia and ketonemia of the SFA-poisoned rats are interpreted as representing diabetes mellitus either secondary to the metabolic effects of SFA on the tissues in general or to a more specific effect of SFA on insulin production by the beta cells of the pancreas.

Fineberg, S. K. (*Diabetic Clin., Harlem Hosp., New York, N. Y.*): CLINICAL EXPERIENCE WITH NPH INSULIN. Am. J. Digest. Dis. *21*:286-88, October 1954.

The author points out advantages of NPH insulin over various mixtures. He finds the action of NPH insulin somewhat less intense than 2:1 mixtures of regular and protamine zinc insulin, and in changing to NPH insulin larger doses are sometimes required. He presents a guide for mixtures of regular and NPH for patients requiring over 100 units of insulin.

Foreign Letters: (*none*): ASSOCIATION OF DIABETICS. J.A.M.A. *156*:1102, Nov. 13, 1954.

A society of diabetics has been formed in Lima, Peru, the second such society to be organized in South America. The Public Health and Social Welfare Ministry is giving it support.

Foreign Letters: (*none*): SUICIDE BY INSULIN. J.A.M.A. *156*:1189, Nov. 20, 1954.

An inquest was held in London, on the death of a 36-year-old nurse who had killed herself by injecting insulin. According to the pathologist who performed the autopsy, death was due to respiratory failure following an overdose of insulin. Although homicide by using insulin has been described in detective fiction, this is said to be the first case of insulin suicide recorded in the English medical literature.

Friedman, Meyer; and Byers, Sanford O. (*Harold Brunn Inst., Mount Zion Hosp., San Francisco, Calif.*): PATHOGENESIS OF DIETARY-INDUCED HYPERCHOLESTEREMIA IN THE RABBIT. Am. J. Physiol. *179*:201-15, November 1954.

The authors report a comparative study of the processes of cholesterol metabolism in rabbits, a species susceptible to dietary hypercholesteremia, and in rats, a species resistant to dietary hypercholesteremia. The authors' concept of the pathogenesis of this type of hypercholesteremia is also presented.

While the rabbit retained 77 per cent of ingested cholesterol as compared with 46 per cent by the rat, this greater absorption by the former is not the dominant basis for its susceptibility to hypercholesteremia, because the rat does not become hypercholesteremic when its absorption percentage is enhanced by use of cholate to equal that of the rabbit and because the rabbit remains hypercholesteremic when quantitatively its absorption is no greater than that of the rat. Further, the rabbit's hypercholesteremia does not result from a more rapid rate of endogenous cholesterol synthesis since studies with Triton WR1339, which inhibits egress of cholesterol from plasma, reveal the rat to synthesize cholesterol more rapidly.

The primary cause of the greater susceptibility of the rabbit to hypercholesteremia appears to be its difficulty in ridding its plasma of cholesterol absorbed from the diet. Induction of equivalent hypercholesteremia by intravenous administration of hypercholesteremic serum is followed by return to normocholesteremic levels within 12 hours in the rat and by persistence of elevated levels at 72 hours in the rabbit. Although the rabbit lacks mast cells and thus may be deficient in heparin, parenteral heparin administration did not hasten the disappearance of hypercholesteremia brought about either by injection or by dietary feeding. Plasmapheresis experiments re-

vealed no factor in rat serum which protected the rabbit against dietary hypercholesteremia and no factor in rabbit serum which provoked this state in the rat.

The use of India ink by intravenous injection to outline the reticulo-endothelial system and of Sudan III and polarized light to visualize fat and cholesterol deposition demonstrate in the rabbit a lesser number of reticulo-endothelial cells and decreased content of lipid and cholesterol. This histologic evidence that the hepatic reticulo-endothelial cells in the rabbit participated relatively little in the disposition of cholesterol is reinforced by chemical studies of the hepatic cholesterol content which indicate that the liver is unable to remove dietary excess of cholesterol from plasma as rapidly in the rabbit as in the rat. The fact that the liver sections in the rabbit showed far fewer fat and cholesterol deposits is interpreted to indicate deficiency of uptake rather than failure to convert or destroy cholesterol by the parenchymal cells.

Because the authors had demonstrated in rats that the hepatic reticulo-endothelial cell played a crucial role in the transfer of dietary cholesterol from the plasma to the liver, a similar role is postulated for this cell in rabbits in the production of dietary hypercholesteremia. Support for this view is derived from experiments in which administration of India ink to rats to block their reticulo-endothelial system is followed by hypercholesteremia, chilomicronemia and plasma turbidity after cholesterol feeding.

Gourley, D. R. H.; and Fisher, Kenneth C. (*Dept. of Zoology, Univ. of Toronto, Toronto, Canada*): ROLE OF CITRATE IN STIMULATION OF OXYGEN CONSUMPTION BY INSULIN IN FROG MUSCLE. Am. J. Physiol. *179*: 378-85, November 1954.

In a study of the respiration of isolated intact skeletal muscle of the frog, the authors observed that both citrate and lactate increased the rate of oxygen consumption and that at any given molar concentration lactate produced the greater acceleration. Frog muscles in Ringer's solution containing citrate become spontaneously active as a result of the reduction of ionized calcium content with a consequent formation of lactate by muscular contracture.

Insulin enhances the rate of oxygen consumption of muscle in Ringer's solution both with citrate and lactate. If the rate in Ringer's solution be taken as 100, then the rate in the presence of lactate is 150, and the rate in the presence of both insulin and lactate is 270. This effect by insulin results from a concentration in the medium as low as 3.0×10^{-2} units per ml.; no effect was produced by 10^{-3} units per ml. Heating the hormone destroys both its ability to lower the blood sugar when injected into mice and its action on the oxygen consumption of muscle. The concentrations of insulin required to produce systemic effects and enhance isolated muscle oxygen consumption are identical and in the quantitative range of catalytic actions. It is probable that the effect of insulin upon the oxygen consumption of isolated frog muscle in the presence of citrate is mediated by the production of lactate as a consequence of the citrate induced muscular activity.

Gray, Doris E.; and DeLuca, H. A. (*Dept. of Biochem., Univ. of Western Ontario, London, Ontario, Canada*): AN ANTAGONISTIC ACTION BETWEEN VITAMIN E AND ALLOXAN IN CARBOHYDRATE METABOLISM OF RAT DIAPHRAGM. Arch. Biochem. *54*:534-40, February 1955.

The authors show that alloxan-washing inhibits glucose uptake, glycogen synthesis, and oxygen uptake by diaphragm isolated from vitamin E-deficient rats, and that this inhibitor can be partly overcome by adding vitamin E to the diet. An antagonistic action of vitamin E and alloxan is suggested.

Grimson, T. A.; and Yell, Joan (*Durham Group of Hosps. and Dryburn Hosp., Durham, England*): SPONTANEOUS HYPOGLYCEMIA DUE TO ISLET-CELL TUMOUR OF THE PANCREAS. Lancet *1*:334, Feb. 12, 1955.

A case of islet cell tumor is presented. The adenoma found had an unusual white color.

Grissom, Robert L.; and Rosenlof, Robert C. (*Dept. of Med., Univ. of Nebraska, Coll. of Med., Omaha, Nebr.*): THE MANAGEMENT OF THE NEW ADULT DIABETIC. Nebraska M. J. *39*:461-65, November 1954.

The patient with diabetes should entertain a hopeful attitude about his disease. With improvement in nutrition and loss of obesity, he will feel better and have a good prognosis for a happy and successful life. It has been well established that the more the patient knows about his disease the better off he is, and it should be

our responsibility as physicians to make sure that he does know as much about his disease as it is possible for us to teach him.

Grom, E.; Erasmo Rodriguez, R. (*none given*): THE NONSPECIFICITY OF SOME OCULAR SYMPTOMS, AND SELYE'S ADAPTATION SYNDROME IN OPHTHALMOLOGY. Arch. Soc. oftal. hispanoam. *14*:555-89, May 1954 (Abstr. in Am. J. Ophth. *39*:117-18, January 1955).

The authors review the literature on the adaptation syndrome, in general, and on its manifestations in the eye, including diabetic retinopathy associated with Kimmelsteil-Wilson disease, and retrolental fibroplasia.

Guild, Harriet G.; Grubb, Wilson; Chu, Mildred Y. F.; and Sidbury, James B. (*Harriet Lane Home, Johns Hopkins Hosp., and Dept. of Pediat., Johns Hopkins Univ., Baltimore, Md.*): VASCULAR COMPLICATIONS OF JUVENILE DIABETES. ANALYSIS OF FORTY PATIENTS AFTER TEN YEARS OF DISEASE. J. Pediat. *41*:722-39, December 1952.

Vascular complications of diabetes, especially those that can be detected in the retina, may be found relatively early in the course of juvenile diabetes.

While the incidence of such complications increases with the passage of time, the time of appearance, severity of lesions, and rapidity of progression are modified by the degree of diabetic control.

Patients with only fair or poor control may show lesions as early as ten years after onset and rarely escape some evidence of vascular damage by the time the disease has been in progress for fifteen years.

Patients consistently well controlled may remain free of lesions for as long as eighteen years and may show no more than minimal changes of doubtful significance as long as twenty-two years after onset. Even in those who do not escape completely, the first appearance of lesions is delayed, and the lesions are less rapidly progressive than in the other groups.

Gurling, K. J.; Robertson, J. A.; Whittaker, Hermon; and Oakley, Wilfrid (*Diabetic Dept., King's College Hosp., Denmark Hill, London, England*): TREATMENT OF DIABETES MELLITUS WITH INSULIN ZINC SUSPENSION. A CLINICAL STUDY BASED ON 479 CASES. Brit. M. J. 71-74, Jan. 8, 1955.

Insulin zinc suspension (insulin lente) was used in the treatment of 479 patients. In less than 7 per cent, was the use of this type of insulin unsatisfactory.

Helmreich, Ernest (*Inst. for Organic Chem. and Polyclin., Sch. of Med., Univ. of Munich, Munich, Germany*): ANIMAL EXPERIMENTS WITH A BLOOD SUGAR LOWERING, ORALLY EFFECTIVE SUBSTANCE FROM ASPERGILLUS NIGER. Klin. Wchnschr. *29*:375-77, June 1, 1951 (Abstr. from: Deutsche med. Wchnschr. *76*:1288, Oct. 12, 1951).

The author believes that blood sugar levels could be lowered significantly in healthy as well as alloxan diabetic rats with a substance obtained from cultures of *Aspergillus niger*.

Landaburu, P. B.; Dávalos, R. C.; Jolly, C. H. (*none given*): THE RELATIONSHIP BETWEEN THE SEVERITY AND CARE OF DIABETES MELLITUS AND THE INCIDENCE OF DIABETIC RETINOPATHY. Arch. oftal. Buenos Aires *29*:7-21, January 1954. (Abstr. in Am. J. Ophth. *38*: 607, October 1954).

A careful statistical analysis of 100 patients who were known to have diabetes mellitus for no less than 10 years leads the authors to adhere to the opinion that, all other factors being equal, retinal changes are more apt to occur in poorly treated patients than in those submitted to prompt, efficient treatment, adequate from the start and continued without interruption.

Lawrence, R. T. B.; Salter, James M.; Best, Charles H. (*Dept. of Physiol., Banting and Best Dept. of Med. Res., Univ. of Toronto, Toronto, Canada*): THE EFFECT OF INSULIN ON NITROGEN RETENTION IN THE HYPOPHYSECTOMIZED RAT. Brit. M. J. *2*:437-39, Aug. 21, 1954.

In a study of hypophysectomized rats, it was shown that insulin causes a markedly positive nitrogen balance as compared to the untreated hypophysectomized controls. There was an approximate linear relation between the retained nitrogen and administered insulin. The experimental results suggest that insulin can function as a growth hormone in the absence of pituitary factors.

Leicher, F. (*Berlin, Germany*): HYPOPHYSEAL CHANGES FOLLOWING ELECTROCOAGULATION. Arch. Klin. Chir. *278*:301-11, 1954 (Abstr. in J.A.M.A. *156*:1363, Dec. 4, 1954).

Percutaneous transfrontal electrocoagulation of hypophyseal tumors suggested by Bauer in 1950 was employed successfully by the author for the first time in a patient with acromegaly, visual disturbances, goiter, hypertension, and diabetic symptoms. With suitable current strength, the electrocoagulation seems suitable for the treatment of primary tumors of the hypophysis.

Mackler, Bruce; and Guest, George M. (*Children's Hosp. Res. Found. and Dept. of Pediat., Univ. of Cincinnati, Cincinnati, Ohio*): BLOOD GLYCOLYSIS: MECHANISMS INHIBITED BY ACIDOSIS. Am. J. Physiol. *174*: 269-72, August 1953.

Changes in glycogen and pyruvate levels and in rates of oxygen consumption of blood during glycolysis are small and apparently are not significantly different in blood with normal and low *p*H. The ratio between glucose disappearing and lactic acid formed as an end-product of glycolysis seems to be the same in normal and in acidotic blood.

The results of these studies suggest strongly that acidosis slows the rate of glycolysis in blood by inhibiting the initial phosphorylation of glucose (probably an effect on the activity of hexokinase) rather than by affecting enzymatic reactions in later stages of the glycolytic cycle.

Manning, Phil R.; and Walford, Roy L. (*Med. Serv. and Lab. Serv. U. S. Air Force Hosp., Chanute Air Force Base, Ill.*): LACK OF EFFECT OF FAT INGESTION ON BLOOD COAGULATION. Am. J. M. Sc. *228*:652-55, December 1954.

The oral ingestion of varying amounts and types of fat caused no statistically significant change in the blood coagulation time, prothrombin consumption time, and clot retraction.

Marble, Alexander (*Harvard Med. Sch., Joslin Clin., New England Deaconess Hosp., Boston, Mass.*): THE MANAGEMENT OF DIABETES IN CHILDHOOD. Nebraska M. J. 39:455-60, November 1954.

It has been estimated that in the United States there are about 17,000 to 22,000 children under the age of fifteen with clinically recognizable diabetes or about 1 in 2,500 individuals in this age group. Now that these patients are kept alive by treatment, the total number of persons with onset of diabetes under the age of fifteen has been estimated conservatively as between 40,000 and 60,000. Thus the problem is a significant one, and one which will continue to grow.

Dietary regulation is important for all diabetics but doubly so for children. In orienting one's thinking, one must have in mind that regulation implies not only certain restrictions but also care that the diet be completely adequate in protein, minerals, vitamins, and calories so that normal growth and development are assured. Some have advocated a "free diet," but such treatment is apt to be no treatment at all and to result in frequent glycosuria and hyperglycemia and high incidence of complications both acute and late. The free diet is mentioned only to condemn it.

Every diabetic child needs insulin and should receive it continuously from the day of diagnosis. Because of his tendency to hyperglycemia even though fasting, he requires insulin not only for the utilization of ingested food but also for continuous, basic control of the diabetic state.

The important acute complications of juvenile diabetes are attacks of hypoglycemia and diabetic coma. One tries to avoid insulin reactions, but if careful control of diabetes is sought, it is difficult to prevent their occasional occurrence. Infrequent mild reactions are not harmful in a physical sense but they are annoying and may tend to shake the patient's confidence. Care in the regulation of insulin dosage, constancy of diet, reasonable constancy of physical activity, and the giving of between-meal and bedtime feedings will do much to decrease the frequency of reactions.

The management of juvenile diabetes resolves itself into just as careful day-by-day control of the condition as can be obtained. Compromises with ideal treatment must often be made because of practical considerations. However, these need not make one lose sight of the goal which is to bring about physiological conditions in so far as possible. Only in this way can the late degenerative complications be prevented and the juvenile diabetic be allowed to live out a useful life span approaching that of the nondiabetic.

Maske, Helmut (*Second Med. Clin., Univ. of Munich, Munich, Germany*): ON THE DIMINUTION OF PENICILLIN ACTIVITY BY THE SERUM OF DIABETICS. Verhandl. deutsch. Gesellsch. inn. Med. *58*:99-101, 1952.

After injection of 300,000 units of procaine penicillin, the penicillin level in the blood of diabetics rose less and then fell more rapidly than in the blood of non-diabetics. This was also observed in well-compensated cases of diabetes without increased diuresis. In vitro tests showed that in a large proportion of diabetics, their serum decreases the activity of penicillin. (German)

Maske, Helmut; and Wolff, Hanns (*Munich, Germany*): INVESTIGATION ON THE HEMOLYSING EFFECT OF VARIOUS DIABETOGENIC SUBSTANCES. Verhandl. deutsch. Gesellsch. inn. Med. 58:763-65, 1952.

Intravenous injection of alloxan or of dithizon (diphenylthiocarbazon) into test animals increased the serum zinc content more than 100 per cent. This increase was followed by a massive increase in the zinc elimination through the urine. The cause of this increase in serum zinc is hemolysis. In 100 cc. of blood, there are contained about 120 gamma serum zinc and 300 to 500 gamma zinc in the erythrocytes, in the latter in water soluble form. Alloxan, alloxantin and dithizon liberate zinc from the red blood cells by hemolysis.

The only quality which these different diabetogenic agents have in common is their combining power with heavy metals, especially zinc. (German)

McCullagh, E. Perry; Fawell, William N.; and Lane, Fenton J. (*Cleveland Clin. Foundation, Cleveland, Ohio, and Frank E. Bunts Educational Inst., Corona Del Mar, Calif.*): SIGNIFICANCE OF HYPERGLYCEMIA WITHOUT GLYCOSURIA. A TEN TO TWENTY-EIGHT YEAR STUDY. J.A.M.A. *156*:925-29, Nov. 6, 1954.

Mild or early diabetes may be manifested by hyperglycemia without sugar in urine. The routine blood sugar test is valuable in detecting diabetes. It is recommended that any patient who consistently has hyperglycemia, even though mild, should have diabetic management and possible aggravating factors corrected in an attempt to decrease the chance of a severer diabetic state developing. Such management is much more important if one or more of the following conditions are present in addition to the hyperglycemia: (1) a family history of diabetes mellitus, (2) obesity, or (3) an age of more than 50 years.

Medical News (*none*): NEW ENGLAND DIABETES FAIR. J.A.M.A. *156*:1094, Nov. 13, 1954.

The fifth annual Diabetes Fair, sponsored by the New England Diabetes Association, was held November 16 and 17, during National Diabetes Week in Boston. Dr. Harry Blotner, chairman of the committee on diabetes detection, stated that nearly 100 new cases of diabetes have been found at each fair.

Melissinos, K.; Katsaros, I. (*First Med. Clin., Univ. of Athens, Athens, Greece*): PATHOGENESIS OF THE DISTURBANCE IN THE BLOOD-SUGAR REGULATION AFTER GASTRECTOMY (A RESEARCH STUDY). Am. J. Digest. Dis. *21*:288-92, October 1954.

Glucose tolerance tests carried out on 21 patients following gastrectomy for gastroduodenal ulcer were abnormal in a high percentage. This was thought to be a result of a disturbed function of the autonomic nervous system.

Melton, G. (*Highlands Gen'l. Hosp., London, England*): TREATMENT WITH INSULIN ZINC SUSPENSIONS. Brit. M. J. *2*:448-49, Aug. 21, 1954.

Sixteen new cases of diabetes were satisfactorily controlled with insulin zinc suspensions. Of 36 old patients previously managed with mixtures of long-acting insulin and soluble insulin or multiple doses of soluble insulin, 26 were satisfactorily controlled with insulin zinc suspension alone and 4 reasonably well controlled with insulin zinc suspension mixtures. Six patients responded poorly to insulin zinc suspensions.

Meng, H. C.; Hollett, Charlotte; and Cole, Walter E. (*Dept. of Physiol., Vanderbilt Univ. Sch. of Med., Nashville, Tenn.*): SOME FACTORS AFFECTING THE CLEARING OF NEUTRAL FAT EMULSION BY POST-HEPARIN PLASMA. Am. J. Physiol. *179*:314-18, November 1954.

A method to determine the clearing of a synthetic neutral fat (triglycerides) emulsion in vitro by the lipemia-clearing factor of postheparin plasma is described. The

quantity of lipemia-clearing factor produced in vivo depends on the dose of heparin injected. The relationship is linear between 0.0 to 0.05 mg. of heparin per kg. of body weight. With administration of larger doses of heparin, the clearing activity in vivo persisted longer but without significant increase in the magnitude of clearing. The clearing factor of postheparin plasma of dogs is thermolabile, but relatively stable at 0°-5° C. The properties of clearing reaction are as follows: (a) optimal *p*H, 6.4 to 7.0; (b) optimal temperature, 35° to 40° C.; (c) higher initial clearing rate during the course of incubation; (d) optimal substance concentration: neutral fat emulsion, 0.32 to 0.72 mg. per ml.; lymph fat, 0.48 to 1.0 mg. per ml.; and (e) clearing activity increased by the addition of sodium acetate.

Mulder, A. G.; Gatz, Arthur J.; and Tigerman, Blanche (*Depts. of Physiol. and Anat., Stritch Sch. of Med. and Graduate Sch., Loyola Univ., Chicago, Ill.*): PHOSPHATE AND GLYCOGEN DETERMINATIONS IN THE HEARTS OF VITAMIN E-DEFICIENT RABBITS. Am. J. Physiol. *179*: 246-48, November 1954.

Cardiac tissue analyses of vitamin E-deficient rabbits exhibited a marked reduction in the creatine phosphate fraction without significant variation in the adenosine polyphosphate or glycogen content. The greatest decrease in creatine phosphate occurred in rabbits whose onset of dystrophy and weight loss were rapid.

Myerson, Ralph M.; and Pastor, Bernard H. (*Med. Serv., Veterans Administration Hosp., Philadelphia, Pa.*): THE FANCONI SYNDROME AND ITS CLINICAL VARIANTS. Am. J. M. Sc. *228*:378-87, October 1954.

The Fanconi syndrome results from a defect in function of the proximal convoluted tubules of the kidney leading to faulty reabsorption of glucose, phosphate, amino acids and occasionally water, bicarbonate, and potassium.

It appears likely that the Fanconi syndrome is one of a fairly large group of disorders which have as their common denominator faulty resorptive function of the proximal tubules. Unifactoral deficiencies involving faulty reabsorption of water, glucose, amino acids, phosphate, and possibly bicarbonate result in the clinical syndromes of nephrogenic diabetes insipidus, renal glycosuria, Wilson's disease (hepatolenticular degeneration), cystinuria, and possibly hyperchloremic acidosis. Multifactoral deficiencies are more difficult to define but appear to include the Fanconi syndrome and cystinosis.

The Fanconi syndrome is rare in the adult. The authors report the case of a man, 56 years of age, in which the diagnostic criteria were present.

Therapy of these syndromes predominantly is a matter of replacement of the material lost because of the resorptive defect. Recently 400,000 units of vitamin D daily have been reported to influence favorably the phosphaturia, glycosuria, aminoaciduria, and the hyperchloremic acidosis of two cases of Fanconi's syndrome.

Nadler, Carl S. (*The Dept. of Med., Tulane Univ. of Med., New Orleans, La.*): RECENT ADVANCES IN POTASSIUM METABOLISM. Am. J. M. Sc. *226*:88-103, July 1, 1953.

The author reviews recent advances in the role of potassium in health and disease, covering distribution of the ion in the body, the dynamics of its transfer across cellular membranes, its intake and output particularly in renal disease, and abnormalities in serum and intracellular concentration in various disease states and their management.

Nelson, H. Bristol; Gillespie, Luke; and White, Priscilla (*Dept. of Obstetrics, Harvard Med. Sch., Joslin Clin., and Boston Lying-in Hosp., Boston, Mass.*): PREGNANCY COMPLICATED BY DIABETES MELLITUS. Obst. & Gynec. *1*:219-25, February 1953.

Creditable results in diabetic pregnancies are dependent upon early and specialized prenatal care. This must include careful control and observation of the diabetes and an awareness of the frequency of complications, with their early recognition and intensive treatment. There is also the realization that early delivery is required in many patients with diabetes, especially when complications develop and the patient fails to respond to therapy. Although agreement does not exist among obstetricians regarding the value of female sex hormone therapy, the authors feel that most diabetics have some imbalance of their sex steroids, indicated by an abnormal rise in chorionic gonadotropin and a low value in urinary estrogens and the urinary metabolite of progesterone metabolism, pregnandiol. It has been postulated that stilbestrol is capable of preventing this imbalance by improving utilization of chorionic gonadotropin, therapy increasing by secretory activity of the syncytium. Placental

production of estrogen and progesterone are thus increased, and the increased output of these hormones in turn improves uterine vascularity. Experience has been that female sex hormone therapy has reduced the incidence of spontaneous abortion, decreased the number of premature labors, and greatly reduced the occurrence of toxemia of pregnancy and severe hydramnios.

Nerenberg, S. T. (*Dept. of Pathol., Univ. of Minnesota, Minneapolis, Minn.*): HYDROPIC CHANGES IN BETA CELLS OF ISLETS OF LANGERHANS. EXPERIMENTAL HYDROPIC CHANGES NOT ASSOCIATED WITH DIABETES MELLITUS. A.M.A. Arch. Path. 56:75-78, July 1953.

Relatively simple and consistent methods for producing hydropic changes in the beta cells of the islets of Langerhans not associated with diabetes mellitus have been described. The experiments described in this paper lend support to the idea that the hydropic change is a "strain" phenomenon. Hydropic changes in the islets of Langerhans should no longer be considered as pathognomonic of diabetes mellitus in animals.

Neubauer, Richard A.; and Garrigues, Elizabeth (*Med. Res. Dept., Memorial Hosp., Wilmington, Del.*): CERTAIN OBSERVATIONS ON THE UPTAKE OF BASE IN UREMIA AND ACIDOSIS DUE TO ADVANCED RENAL DISEASE. Am. J. M. Sc. 228:656-67, December 1954.

Eight cases of advanced renal failure (glomerulonephritis, polycystic kidneys, pyelonephritis) were reviewed as to potential mechanisms which would produce a body deficit of base.

Data for the intake and output of sodium, potassium, and chloride during the administration of supplementary electrolytes showed in most cases varying degrees of body base deficit not reflected in the serum sodium and potassium values. The history or clinical condition of the patient did not present a reliable guide to the magnitude of cation depletion at the time of the metabolic study. When sodium was administered as hypertonic sodium lactate in these cases, the excretion of sodium in the urine appeared to be intimately related to the anion.

Neubert, Frank R. (*none given*): VASCULAR PATTERNS IN THE EYE. (A PRELIMINARY REPORT ON A PHOTOGRAPHIC STUDY.) Tr. Ophth. Soc. U. Kingdom 73:251-60, 1953 (Abstr. in Am. J. Ophth. 38:591, October 1954).

A report is made of a photographic study of the vascular patterns in infection of the eye, to see whether the vessels behaved similarly in tuberculosis, diabetes, syphilis, or in hyperpiesis, and if the diagnosis could be influenced by the pattern which they made. These hopes were not substantiated.

Niemeyer, Hermann; and Figueroa, Enrique (*Inst. of Chem., Physiol., and Path., Sch. of Med., Univ. of Chile, Santiago, Chile*): INFLUENCE OF GLYCOGEN CONTENT ON THE EFFECT OF 2, 4-DINITROPHENOL ON THE OXYGEN UPTAKE BY RAT LIVER SLICES. Arch. Biochem. 54: 135-45, January 1955.

In studies on the rat liver the authors demonstrate a decreased oxygen uptake when DNP (2,4-dinitrophenol) is added to livers with low glycogen content, and an incomplete uptake when the glycogen content was 2 per cent or more. The inhibitory effect on respiration of DNP could be modified in the presence of various substrates.

Oakley, Wilfrid (*Diabetic Dept., King's Coll. Hosp., London, England*): THE MEDICAL ASPECTS OF THE EMPLOYMENT OF DIABETICS. The Transactions of the Association of Industrial Medical Officers 4:48-51, July 1954.

It is good policy to encourage employers to regard diabetics as normal men and women. This is a justifiable attitude from the efficiency point of view. Although diabetes is controllable, it may entail a real disability. Most diabetics are relatively normal useful citizens and not severely handicapped. They should not be petted or pitied because their daily routine includes one or two injections of insulin. The fact that insurance companies and employers sometimes refuse to take the same enlightened outlook is apt to make the sufferer from diabetes pessimistic about the social consequences of his complaint. In order to keep fit, the diabetic working man or woman must observe rules in regard to (1) regular insulin, (2) regular meals, (3) regular exercise, and (4) regular supervision. These are the four golden rules, and efforts should be made to make it possible and easy for diabetics to observe them.

Ortmeyer, Donald W.; and Jackson, Robert L. (*Broadlawns Polk County Hosp., Des Moines, Iowa, and Dept. of Pediat., Univ. of Missouri, Columbia, Mo.*): MORTAL-

ITY STUDY OF YOUNG DIABETIC PATIENTS. J. Iowa M. Soc. *45*:137-44, March 1955.

Case histories of 40 deaths, in a group of 411 juvenile diabetic patients observed at the State University of Iowa Pediatric Clinic from 1920 to 1950, are presented. Causes of death included: infection 39.3 per cent; diabetic acidosis 28.6 per cent; kidney disease 10.7 per cent; tuberculosis and accidental death each 7.1 per cent; and hypoglycemia and vascular accident each 3.6 per cent. Infection or diabetic acidosis accounted for the majority of deaths in patients who had had diabetes less than ten years; cardiovascular-renal disease accounted for 40 per cent of the deaths in patients who had had diabetes more than ten years.

The majority of the patients maintained fair-to-poor control of their diabetes and had poor social and economic backgrounds.

Autopsy findings indicate that no significant cardiovascular-renal pathology occurs in patients who have had poorly controlled diabetes less than ten years.

Pattison, D. Stanley (*Dept. of Obst. & Gynec., Medicine Hat Gen. Hosp., Medicine Hat, Alberta, Canada*): INDUCTION OF LABOR, INDICATIONS AND METHODS. Am. J. Obst. & Gynec. *69*:233-39, February 1955.

When pregnancy is complicated by diabetes mellitus, the author believes induction of labor prior to the thirty-sixth week of pregnancy provides the lowest fetal mortality rate.

Paullada, Juan José (*Mexico*): EVALUATION OF TESTS FOR ADRENAL INSUFFICIENCY. Rev. invest. clín. *6*:249-66, April-June 1954 (Abstr. from J.A.M.A. *156*:557-58, Oct. 2, 1954).

Hypoglycemia was found in 38 per cent of the patients with primary hypoadrenalism and in 40 per cent of the patients with secondary adrenal insufficiency. Fifty per cent of the patients with primary hypoadrenalism showed a flat curve. Of the five patients with secondary adrenal insufficiency four had a flat curve. The author concludes that the most useful tests for primary or secondary adrenal insufficiency are: (1) the determination of 17 ketosteroids, (2) the lack of increase of these compounds after the intramuscular injection of 20 units of corticotropin, (3) the degree of lymphocytosis, (4) the test for water elimination, and (5) the absence of or a decrease of more than 50 per cent in eosinophils after an intramuscular injection of 20 units of corticotropin.

Pearson, Seibert (*Long Beach, Calif.*): ABERRANT PANCREAS: REVIEW OF THE LITERATURE AND REPORT OF THREE CASES, ONE OF WHICH PRODUCED COMMON AND PANCREATIC DUCT OBSTRUCTION. A.M.A. Arch. Surg. *63*:168-84, August 1951.

A review of the literature on aberrant pancreas and a historical summary of the subject are presented. The cases reported through 1950 have been collected, and the embryology and theories of origin have been reviewed. The pathology, physiology, and symptomatology are discussed. Three case reports are presented, including what is believed to be the first successful removal of aberrant pancreas in the ampulla of Vater, which produced obstruction of the common and pancreatic ducts.

Pedowitz, Paul; and Shlevin, Edmund L. (*Depts. of Obst. & Gynec. & Med., State Univ. of New York, New York, Coll. of Med., and Jewish Hosp., Brooklyn, N. Y.*): THE PREGNANT DIABETIC PATIENT. Am. J. Obst. & Gynec. *69*:395-404, February 1955.

A series of 78 pregnancies, observed from Jan. 1, 1950, to Dec. 31, 1953, is reported. There were 73 reaching viability. The fetal loss was 8.2 per cent. There was an 11.4 per cent fetal loss in 44 cases belonging in Group B. of White's classification. Acidosis occurred in 28.7 per cent of the cases. In the group with acidosis, there were 3 stillbirths and 1 neonatal death. Preeclampsia occurred in 14.9 per cent of the cases. Four infants were lost of the 10 patients developing diabetes during pregnancy.

Prenatal care is discussed. Obstetrical management included delivery by the 37th week, Cesarean section being the method of choice in the majority of cases (63 per cent). It is suggested that substitutional hormone therapy is of no value.

Penhos, J. C. (*Buenos Aires, Argentina*): DIABETOGENIC ACTION OF GLUCAGON. Ciencia e Investigación *10*:365, August 1954.

The diabetogenic action of cortisone in rats is potentiated by the administration of glucagon. Cavallero studied changes in carbohydrate metabolism in three groups of

rats given cortisone, glucagon, and cortisone-glucagon respectively. Glycosuria was observed only in the group treated with glucagon-cortisone seven to nine days after beginning the administration. Likewise, a high fasting blood sugar was observed in this group in comparison with the others. (Spanish)

Pessoa, V. C.; Kim, K. S.; and Ivy, A. C. (*Dept. of Clin. Science, Univ. of Illinois Coll. of Med., Chicago, Ill.*): Fat Absorption in Absence of Bile and Pancreatic Juice. Am. J. Physiol. *174*:209-18, August 1953.

Experiments have been conducted to determine the mechanism by which normal dogs absorb various fats and fatty acids and to evaluate the importance of the external secretion of the liver and pancreas in this activity. The endogenous-lipid excretion has been found to be approximately 39.4, 142 and 125 mg. per kg. per day for normal, biliary-fistula and pancreatic-duct-ligated dogs respectively. Normal dogs absorbed triglycerides and fatty acids better than dogs deprived of bile or pancreatic juice. However, a considerable amount (70 per cent) of neutral fat, as corn oil, and of fatty acid (55 to 75 per cent), as corn-oil-fatty acids and oleic acid, is absorbed in the absence of bile or pancreatic juice which shows that neither bile nor pancreatic juice is indispensable for the absorption of any of the fats and fatty acids studied. A low-melting-point fat which consists mainly of unsaturated fatty acids, as corn oil, is better absorbed than a fat of high melting point and consisting of saturated fatty acids, as tallow fat, in pancreatic-duct-ligated dogs and to a less extent in biliary-fistula dogs. This conclusion is based on preliminary observations and should be studied further.

Queries and Minor Notes (*none given*): Intravenous Glucose Solution Infusion. J.A.M.A. *152*:881, June 27, 1953.

In a study conducted a number of years ago, no dehydrative effect was produced by an injection of either 10 per cent or 5 per cent dextrose in water, about 3,000 cc. being given intravenously at the rate of 300 to 500 cc. per hour. With the 5 per cent dextrose solution, 80 per cent of patients had glycosuria, but, on the average, only 3 gm. of sugar per day were recovered in the urine. With the 10 per cent dextrose solution, all the patients were glycosuric, but the urine sugar loss averaged only 18 gm. per day. The latter solution is, therefore, of distinct value when more calories are needed as in cases of undernutrition or damaged liver requiring support. The caloric value per day of the 10 per cent solution was almost double that of the 5 per cent solution, and for this reason it is valuable.

Queries and Minor Notes (*none*): Myocardial Infarction. J.A.M.A. *156*:1036-37, Nov. 6, 1954.

When recent myocardial infarction occurs in a diabetic, it may be advisable to use regular insulin and not depot insulin in order to avoid unpredictable hypoglycemic periods.

Randle, P. J. (*none given*): Assay of Plasma Insulin Activity by the Rat-Diaphragm Method. Brit. M. J. *1*:1237-40, May 29, 1954 (Abstr. from Am. J. Digest. Dis. *21*:299, October 1954).

It was shown by the rat-diaphragm method that the insulin activity of normal human plasma of patients who have had a glucose meal was 13 milli-units per ml. It has been reported that the estimate is higher than it was previously.

Saphir, William (*Chicago, Ill.*): Spontaneous Hypoglycemia in Acute Gastro-Enteritis. Am. J. Digest. Dis. *20*:138-39, May 1953.

The author presents a case of acute gastro-enteritis in which blood sugar values of 55 and 48 mg. per 100 cc. were obtained on consecutive mornings. The author believed that some breakdown in the blood sugar regulating mechanism had occurred. He obtained blood sugar determinations every 30 minutes after an 8-hour fast and a rising curve was obtained.

Schaefer, John H. (*Los Angeles, Calif.*): Value of Routine Laboratory Tests. J.A.M.A. *156*:460, Sept. 25, 1954.

In addition to routine blood counts and urinalysis, the author advises a blood sugar test for every person before major surgery. The author has encountered a number of patients with fasting blood sugar values as high as

400 mg. per 100 cc., in whom the urine was sugar free and diabetes was hitherto unrecognized. A sugar-free urine is no guarantee that the patient is not seriously diabetic. A routine blood sugar test on all candidates for surgery or at the time of hospital admission not only would be a worthwhile safety factor but would provide many surprises.

Schwietzer, Kurt H. (*Hamburg, Germany*): IRON, PROTEIN, HAEMOCHROMATOSIS. Verhandl. deutsch. Gesellsch. inn. Med. *58*:768-71, 1952.

The frequent occurrence of pigment cirrhosis in war prisoners, returning from Russia, directed the attention of the author to the connection between iron metabolism and protein. The importance of two proteins for the iron metabolism is well known. The first is apoferritin which as a colloid envelops ferric hydroxide micellae and prevents the latter from precipitation. To prevent this, under certain conditions, from threefold to tenfold quantity of apoferritin may be necessary. Apoferritin, with the suspended ferric hydroxide micellae, is called ferritin. Iron absorbed from the intestine is stored as ferritin, especially in the liver and spleen.

Lack of protein leads to a reduction of the quantity of apoferritin and finally to a precipitation of the iron in the form of hemosiderin. Freshly precipitated, ferric hydroxide can be used for hemoglobin synthesis, but, after the precipitation, an aging process takes place and gradually the ferric hydroxide crystallizes and becomes inactive and unfit for the building of hemoglobin.

Lack of protein not only leads to precipitation of iron, but also to an increase in iron absorption, because for the transportation of iron, β_1 globulin is needed. Lack of protein in the food leads to a diminution of the albumin fraction of the serum proteins and to an increase in the a_2 and β_1 and β_2 globulin fractions, and consequently also of the iron uptake, which, on account of scantness of apoferritin cannot be stored properly, but is precipitated in the liver cell, destroying the latter, while the iron remains.

To store iron properly, the body needs a sufficient amount of protein. (German)

Semple, Robert (*Middlesex Hosp., London, England*): DIABETES AND PERIPHERAL ARTERIAL DISEASE: A CLINICAL STUDY. Lancet *1*:1064-68, May 30, 1953.

One hundred diabetics, aged more than 50, were examined for the presence of obliterative arterial disease of the legs. Signs of arterial disease were found in 42 per cent, although only 10 per cent had symptoms attributable solely to impaired circulation. The occurrence of arterial disease was related to increasing age but not to the severity or to the duration of the diabetes. Of 52 consecutive cases of gangrene almost half were in diabetics. Arterial disease in diabetics presented more often with gangrene than with intermittent claudication, and the usual site of obstruction was in the more distal vessels of the leg and foot, the femoral and popliteal arteries being clear; in both these respects the reverse held true in nondiabetic arterial disease.

Shay, Harry; and Sun, David C. H. (*Samuel S. Fels Res. Inst. and Temple Univ. Sch. of Med. and Hosp., Philadelphia, Pa.*): STRESS AND GASTRIC SECRETION IN MAN: I. A STUDY OF THE MECHANISMS INVOLVED IN INSULIN HYPOGLYCEMIA. Am. J. M. Sc. *228*:630-42, December 1954.

The authors cite Gray's evidence that stress, corticotropin, and cortisone stimulated gastric secretion in man and the work of Porter, French, and their associates in monkeys that the stress effect of insulin hypoglycemia acting on the posterior hypothalamus initiated reactions that resulted in increased gastric acid secretion and that intact adrenals were necessary for this response to occur. The author's experiments offer support for a similar mechanism in man, and point to the probability that adrenalin is liberated in the stress effect of insulin hypoglycemia and plays an important part in the cycle that results in the stimulation of gastric secretion. Consideration is necessary of an adrenal phase of gastric secretion in the peptic ulcer problem and that this phase is a significant part of the harmful somatic mechanisms activated by stress reactions.

Sherber, Daniel A.; Levites, Murray M. (*New York*): HYPERCHOLESTEREMIA. J.A.M.A. *152*:682-86, June 20, 1953.

In a survey of the serum cholesterol in 960 consecutive patients admitted to the medical services of Fordham Hospital, 13.7 per cent were found to have serum cholesterol values of 300 mg. per 100 ml. or over; 69.5 per cent of the patients with hypercholesteremia had cardiovascular disease, and 20.7 per cent had diabetes. The effect of a polysorbate 80-choline-inositol complex on

the serum cholesterol and protein-bound iodine levels and urinary cholesterol, 17-ketosteroid, and formaldehydogenic steroid excretion in 16 hypercholesteremic patients is reported. In 15 of the 16 patients studied, there was a significant drop in the serum cholesterol level. The use of the polysorbate 80-choline-inositol complex has given some indication of the role of the adrenal cortex in the control of cholesterol metabolism and the influence of the state of the serum cholesterol emulsion on adrenal cortical function.

Smith, M. J. H.; and Taylor, K. W. (*Dept. of Chem. Path., King's Coll. Hosp. Med. Sch., London, England*): BLOOD CONCENTRATIONS OF PYRUVIC AND *a*-KETOGLUTARIC ACIDS IN NORMAL PEOPLE AND DIABETIC PATIENTS. Lancet *1*:27, Jan. 1, 1955.

In studies on eight diabetic patients and seven normal subjects, there was no difference between the blood levels of pyruvic and ketoglutaric acids.

Stowers, J. M.; and Nabarro, J. D. N. (*Dept. of Med., Univ. of St. Andrews, Dundee, Scotland, and Middlesex Hosp., London, England*): CLINICAL EXPERIENCE OF THE INSULIN ZINC SUSPENSIONS. Brit. M. J. *1*:68-71, Jan. 8, 1955.

In a study of 240 patients, the authors conclude that insulin zinc suspension (lente) has definite advantages over other preparations, and that it is satisfactory in the management of 90 per cent of all diabetics requiring insulin. In the majority of patients, a ratio of 3 parts amorphous to 7 parts crystalline proved satisfactory. In 10 per cent of cases, the use of lente insulin was unsatisfactory.

TREATMENT OF DIABETIC RETINOPATHY. (*Presented at a Joint Meeting on Ocular Therapeutics, New York Academy of Medicine, Section on Ophthalmology, & New York Society for Clinical Ophthalmology, Jan. 18, 1954*). Am. J. Ophth. 39:95-96, January 1955.

The majority of diabetics with diabetic retinopathy also have Kimmelsteil-Wilson lesions in the kidney.

Rich has shown Kimmelsteil-Wilson lesions can be induced experimentally by administration of cortisone to rabbits. Becker has reported that in an animal with alloxan diabetes given corticotropin, not only can Kimmelsteil-Wilson lesions be induced, but also lesions which simulate rather closely diabetic retinopathy.

The panel concludes that at the present time we have no adequate methods of preventing or controlling diabetic retinopathy, with the possible exception of good dietary control.

Van Itallie, Theodore B.; Morgan, Mary C.; and Dotti, Louis B. (*Dept. of Med., St. Luke's Hosp., New York, N.Y.*): EFFECT OF GLUCAGON ON PERIPHERAL UTILIZATION OF GLUCOSE IN MAN. J. Clin. Endocrinol. *15*:28-35, January 1955.

Peripheral glucose uptake in normal human subjects during and after glucagon-induced hyperglycemia was compared with peripheral uptake during and after similar hyperglycemias produced (a) by intravenous infusion of glucose, and (b) by ingestion of glucose following subcutaneous injection of epinephrine. Peripheral glucose capillary-venous differences were determined serially throughout each experiment and served as indices of glucose uptake by peripheral cells. Comparison of capillary-venous differences following glucagon administration with those following infusion of glucose showed that peripheral utilization of glucose was not inhibited by glucagon. If anything, utilization of glucose may have been enhanced during glucagon-induced hyperglycemia. In contrast, epinephrine injection was followed by apparent inhibition of peripheral glucose uptake. Since glucagon does not inhibit peripheral utilization of glucose, it is suggested that description of glucagon as an "insulin antagonist" is misleading.

Walaas, O.; Lingjaerde, O.; Løken, F.; Hundevadt, E. (*Lier Mental Hosp., Lier and Univ. Physiol. Inst., Oslo, Norway*): THE EFFECT OF SERA FROM SCHIZOPHRENIC PATIENTS ON GLUCOSE UTILIZATION OF THE ISOLATED RAT DIAPHRAGM. Scandinav. J. Clin. & Lab. Invest. *6*: 245-49, 1954.

The sera of three patients with active schizophrenia had less stimulating effects on glucose uptake by isolated rat diaphragms than did sera from normal patients. In one schizophrenic patient improved by insulin coma three months previously, the stimulating effect was similar to that observed in normals.

EDITORIALS

CAMPS FOR DIABETIC CHILDREN

Summer camps for diabetic children are here to stay. It was in the summer of 1929 when Dr. and Mrs. Henry John took a group of diabetic children to camp in their woods 25 miles east of Cleveland. This is the oldest camp in existence in this country, although one did operate near Detroit for some years following 1925 under the direction of Dr. Leonard F. C. Wendt. In 1955 there will be at least 25 camps for diabetic children operating in the United States and Canada. Some of the newer and smaller camps serve perhaps a dozen diabetic children for two weeks while others now serve as many as 100 children a month for three months. The facilities vary greatly; some utilize a portion of kitchen facilities, under the supervision of a nurse and dietitian in a Boy Scout's or a Camp Fire Girl's Camp. Some take over a camp used primarily for other purposes for two weeks with volunteer workers. Still others own their own facilities or are sponsored or owned by a local diabetes association. They all have one common bond, namely, an interest in the health and happiness of the diabetic child.

The value of a session at camp for most diabetic children is immense. The average diabetic child because of necessary restrictions is denied the pleasure and freedom of living and playing with his friends at camp. Many diabetic children carry a heavy psychological burden, sometimes because of poor adjustment to the difficulties imposed by their disease but perhaps as often transferred to them by tense and over-anxious parents. Sometimes they have suffered in health as well as in mind through the pity or overindulgence of unwise parents. One needs to live with a child with severe diabetes at camp or at home only for a short time to realize the constant stress which is placed on the mother and what relief is afforded her when her child goes to camp for a few weeks. The change in situation with wise, firm, kind handling is sufficient to aid greatly in the psychological adjustment of most diabetic children.

Much diabetic education can be subtly woven into the many activities at camp, and much teaching of extracurricular subjects can be done. The children learn from their songs and dances, their plays and stunt nights, the dinner speeches, tennis, swimming, hiking, cookouts, archery, and riflery. They learn by direct teaching as well as by observing their nurses, dietitians, counselors, and each other. Many camps have found it useful to become members of the National Archery Association, and the National Rifle Association so that proper scoring and official recognition of merit can be given. Many camps follow the instruction system for life-saving and swimming set by the American National Red Cross. The Junior Audubon Clubs may be useful in setting up nature-study programs.

All camps, big or small, old or young, wrap up as much of this as they can into a neat parcel tied together with the best possible medical, and dietetic care, and dress it all up to look as little as possible like a hospital. Diabetic children who come to camp in poor health leave in good health in almost every instance; and many who never have had the value of good diabetic control may remain in good health, as the result of good medical care at camp, for an indefinite period afterwards.

Medical directors of camps and those interested in training of young men and women in pediatrics or in metabolic disease should not overlook the valuable training which can be gained by them at camp. One month at camp will give more experience in childhood diabetes than most physicians get in a lifetime.

Physicians everywhere who have contact with diabetic children are urged to tell their families about the existence and the value of "Diabetic Camps." If this is done the present capacity of these camps, which is about 2,400, will soon be overreached, and we may hope that before long many hundreds more diabetic children can be helped to be healthier people and happier, better citizens through the efforts of camps.

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THE CONGRESS OF THE INTERNATIONAL DIABETES FEDERATION

The Diabetes Congress to be held in Cambridge, England, July 4 to 8 will mark another landmark in the development of the world-wide campaign against diabetes. Delegates from national diabetes associations will confer on problems of organization. Physicians and research workers will attend scientific programs. Laymen concerned with the problems of diabetes because of their interest in personal and public health will participate in special meetings and demonstrations. Through these activities attention will be given to every phase of diabetes—experimental, clinical, economic and social.

The International Diabetes Foundation which has made arrangements for this Congress is a young organization. Its foundations were laid at a meeting held in Brussels, Belgium, in the summer of 1949, which was attended by leaders in work with diabetes from several countries. It was formally established at the first International Diabetes Congress held in Leiden, Holland, in 1952. Its objectives are to disseminate information regarding diabetes and to serve the interests of diabetics throughout the world. This second Congress represents its most ambitious project in relation to these objectives.

The formation of special organizations concerned with diabetes is the development of the past quarter century. It is believed that the first step was taken in New York City when the New York Diabetes Association was initiated in December 1929. The first national association was The Diabetic Association which had its beginning in London, England, in 1931. Since then local diabetes societies have appeared in approximately forty areas of the United States and national associations are now active in a score of countries. The American Diabetes Association formally established in 1940 is linked with other national organizations in the International Diabetes Federation. Members of our Association can take pride in the fact that Dr. Elliott P. Joslin, Honorary President, and Professor Charles H. Best, Past President, are Honorary Presidents of the International Diabetes Federation. Dr. Howard F. Root, also a Past President, is First President of the Federation.

Our present-day knowledge of diabetes has been accumulated through the efforts of citizens of many countries. This is illustrated by even a partial list of those who have made significant contributions — Willis of England, Langerhans, von Mering and Minkowski of Germany, Laguesse of France, Opie and Bensley of the United States, Banting and Best of Canada, Houssay of Argentina and Hagedorn of Denmark. The international exchange of ideas and experiences through personal contact can facilitate the further development of an understanding of the unsolved problems of diabetes.

A Definition of Diabetes Mellitus

Diabetes is an hereditary disease, characterized by an increase of glucose in blood and the excretion of this sugar in the urine; it is dependent upon a deficient formation or diminished effectiveness of insulin secreted by the beta cells of the islands of Langerhans of the pancreas and is functionally interrelated with conditions arising in the liver and in endocrine glands other than the pancreas particularly the pituitary and also the adrenal and thyroid.

By Elliott P. Joslin, M.D., and Associates, in *Treatment of Diabetes Mellitus,* Philadelphia, Lea and Febiger, 9th ed., 1952, p. 251.

BOOK REVIEWS

A GUIDE IN DIABETES. *By Rosario Robillard, M. D., Physician in charge of the Diabetic Clinic, St. Luke's Hospital, Assistant Clinical Professor of Medicine, University of Montreal, Cloth. $4.75, pp. 282 with illustrations. R. Robillard, 532 Cherrier St., Montreal, Canada, May 1955.*

This book should be welcomed by French-speaking diabetic patients and physicians for it is the first of its kind to be written in the French language by a Canadian. The author successfully reaches his stated objective, the preparation for diabetic patients, medical practitioners and students and nurses of a relatively concise guide in diabetes with an outline of its treatment and a discussion of its complications. Throughout the book, the author emphasizes the importance of continuous instruction of diabetic patients and also tactfully indicates the needs of medical practitioners. Pitfalls in diagnosis and treatment of diabetes are presented. This book merits a place in the library of every physician with French-speaking patients in either Canada or the United States.

HYPOGLYCEMIA AND THE HYPOGLYCEMIC SYNDROME. *By A. J. Kauvar, M.D., Assistant Clinical Professor of Medicine, University of Colorado School of Medicine; Attending Physician Gastro-Enterology, Colorado General Hospital and Denver General Hospital, and Martin G. Goldner, M.D., Clinical Associate Professor of Medicine, State University of New York, Medical Center at New York; Director of Medicine, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N. Y. $3.00, pp. 67. Charles C. Thomas, Publisher, Springfield, Ill.*

The authors present a review of the literature based on 1953 selected publications including four by one of the authors. The book includes a brief historical review beginning with the observation of low blood sugar levels by Minkowski when he removed the liver from an experimental animal. The latest publications referred to appeared in 1953. The chapter titles include: "The Causes of Hypoglycemia," "Differential Diagnosis of the Hypoglycemic Syndrome," and "Management of the Hypoglycemias and of the Hypoglycemic Syndrome."

A table showing the fasting blood sugar level of various species is interesting. In most mammals, the blood sugar is usually about the same as in man; exceptions include the ruminants with the blood sugar value about half this amount, and the pig with a blood sugar range of 40 to 200. The blood sugar of birds is high (chick, duck and goose 150 to 200, pigeon 120 to 140, turkey 175 to 210). The blood sugar of cold-blooded animals varies; the figures for fish are 100 to 120 and for frogs 30 to 45.

PRACTICAL ENDOCRINOLOGY. *By Lewis M. Hurxthal, M.D., Department of Internal Medicine, Lahey Clinic. In cooperation with A. Seymour Parker, M.D., Department of Internal Medicine, Lahey Clinic, and Hirsch Sulkowitch, M.D., Research Associate, Lahey Foundation, Boston, Massachusetts. $7.00, pp. 318. Landsberger Medical Books, Inc., distributed solely by The Blakiston Division of the McGraw-Hill Book Co., New York, N. Y., 1955.*

This book which is the first-published volume in a series of *Handbooks for the General Practitioner* presents in twelve chapters concise discussions of the various diseases of the endocrine glands, including endocrine disorders of infancy and childhood, gynecomastia, hirsutism, the use of steroid and other hormones, and office endocrine laboratory tests. The short readable text containing seventeen illustrations constitutes a practical scientific handbook of endocrinology. As the chief author indicates in the introduction, more details about any certain aspects of endocrinology can be found when necessary by consulting standard textbooks. In the reviewer's opinion this volume is the best of the books on endocrinology that have been prepared for the general practitioner.

Diabetes Mellitus at the Massachusetts General Hospital from 1824 to 1898

A Study of the Medical Records

Reginald H. Fitz, M.D., and Elliott P. Joslin, M.D., Boston

Dr. Elliott P. Joslin laid the foundation for his lifetime interest in diabetes at the beginning of his medical career. The results of his careful study of the early medical records of the Massachusetts General Hospital published in collaboration with Dr. Fitz 57 years ago reveal information of interest from the viewpoint of the medical historian. The paper is also instructive from two other points of view. The importance of careful observation and sound evaluation of clinical data is illustrated. The progress which has been made in the therapy of diabetes since its initial publication represents a challenge to the future.

The examination of the records of the cases of saccharine diabetes treated in the wards of the Massachusetts General Hospital during the past seventy-four years was begun for the purpose of seeking evidence with regard to the pancreatic origin of this disease. Since several hundred volumes were to be searched it seemed desirable to obtain at the same time information upon other points which might contribute to the statistics of diabetes. Facts of interest in diagnosis and treatment were elicited as the study progressed and this paper is offered rather as a historical sketch of the progress of a disease drawn from the original records than as an attempt to advance in any way our knowledge of the subject. Since diabetes mellitus was first sharply differentiated from diabetes insipidus early in the present century, the hospital records may be considered to be nearly as old as is our knowledge of the disease in question.

During these seventy-four years the total number of cases of diabetes mellitus treated in the medical wards was 172, but of these, 9 were readmitted, making 181 separate entries. The following table shows the variation in the number of such patients during successive periods of years and their proportion to the total number of cases treated during the same periods.

Period	Total number of patients	Number of cases of diabetes	Per cent
From 1824 to 1840	5,328	7	.13
From 1840 to 1855	6,136	16	.26
From 1855 to 1870	8,660	24	.27
From 1870 to 1885	11,690	39	.33
From 1885 to 1898	16,085	86	.53

It appears from this table that within the past thirteen years as many cases of diabetes were admitted to the hospital as in the previous sixty-one years and the per cent in the past thirteen years in proportion to the total number of hospital entries has increased fourfold over that of the first fifteen years. This fact is not due to any recent increase in the number of beds open to this class of patients, nor, presumably to any considerable excess in the frequency of this disease in the region from which the hospital receives its patients. Whatever may be its cause this occurrence is to be regarded as evidence of the wholesome tendency of diabetics to place themselves under careful medical supervision for such length of time as shall permit suitable observations to determine the severity and controllability of the disease, that the future conduct of the patient may accordingly be regulated.

Age	Number of cases	Per cent
From 0 to 10 years	3	1.8
From 10 to 20 years	15	8.8
From 20 to 30 years	41	24.1
From 30 to 40 years	43	25.3
From 40 to 50 years	29	17.1
From 50 to 60 years	28	16.5
From 60 to 70 years	11	6.4

Of the 172 cases, 127 (or disregarding fractions, 74 per cent) were males and 45 (or 26 per cent) were females. The oldest patient was 73 years of age and the

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youngest 5 years, the average age of 161 patients being 33.4 years. The average age among 40 female patients was 39.1 years, being higher than that in 121 males in whom it was 31.4 years. The preceding table represents the time of life at which the disease began.

Diabetes thus is shown to be a disease predominantly affecting the middle third of life, though sparing neither the child of five nor senior of seventy-three.

But one of the patients was a negro, a further illustration of the rarity of diabetes in this race, although Tyson (*Practice of Medicine,* 1896, 751) has met with several instances. Ninety-seven of the patients lived in the United States, and 83 claimed this country as their birthplace. Thirty-nine of the patients were born in Ireland, 11 in the British Provinces, 9 in England, 4 in Scotland, 7 in Germany, 2 in Sweden and 1 in Denmark. Forty-three of the patients were mechanics, 23 servants, 17 laborers and 13 farmers. Of merchants there were 5, and of clerks 7. There were 5 mariners and 4 teamsters. Although four of the patients were students there were but two professions represented, a clergyman and an artist being included among the entries. There were single or a few representatives of several other occupations, and conspicuous for its absence was that of liquor dealer.

In 42 cases the question of an inherited tendency to the disease was raised and this factor was stated to have been present in 10 patients and absent in 32. In one case the father died of possible diabetes and this disease was the cause of the death of a brother and his daughter. The brother of one diabetic patient fell upon the ice, striking his head, and died of diabetes four days later. In three of the cases the symptoms of diabetes came on within a few weeks after severe injury.

One of these patients while working in a mill in July so strained his back by lifting a heavy weight that he was unable to accomplish much afterwards on account of supposed weakness of the spine. In August the appetite became increased and in December he entered the hospital for treatment of diabetes. The second was buried in a sand bank three months before entrance and was taken out unconscious. Six weeks later thirst made its appearance as the first symptom indicative of the onset of the diabetes. The third fell fourteen feet and struck on the back of the head. He was unable to work for a fortnight. Very soon afterward he began to have great thirst, hunger, and frequent micturition of large quantities of urine. The disease began in a female patient one month after very hard work in caring for a sick sister. The possibility of contagion was entertained in the case of a servant whose mistress was suffering from a severe variety of diabetes.

Post-mortem examinations were made in 15 of the 47 fatal cases. As is usual in this disease no characteristic lesions were found. The liver generally was normal in appearance although sometimes enlarged and in one instance it was rather small. The kidneys as a rule were normal, were enlarged in one instance, congested and with fat drops in the cortex in another, enlarged and hemorrhagic in a third, enlarged and infiltrated with round cells in a fourth. The stomach was large in two cases and Brunner's glands were found "developed" in a case under the care of Henry I. Bowditch in 1848. The condition of the pancreas was not mentioned in seven of the cases. This gland was stated to be normal in five and small in three instances. In one of the three its tissues were not remarkable, in another there was a moderate infiltration of fat tissue around the head of the gland, and in the third the weight was recorded as an ounce and a half, the section showing a coarsely granular surface.

No attempt has been made to note the relative frequency and the severity of the various symptoms. Particular attention has been paid, however, to the records of the condition of the urine, since they furnish a valuable commentary of the progress of our knowledge concerning the methods of studying this secretion.

In the earliest volumes of the records especial importance was attached to the measurements of the quantity of urine passed as compared with the quantity of liquids ingested, since formerly it was the belief that patients excreted more urine than they drank liquid.

In this connection it is interesting to note that a metabolism experiment in diabetes was made at the hospital in 1845. For it is then recorded that "in the last twenty-four hours ingesta were, solid 30 oz., liquid 54 oz. Total 84 oz. Egesta were, solid 8 oz., liquid 26 oz. Total 34 oz. Difference 50 oz."

The largest quantity of urine stated to have been voided in twenty-four hours was 576 ounces. The record of this patient is, "June 26, 1861, urinated thirty-six times; voided thirty-six pints. . . . It contained 3 per cent of sugar, corresponding to 227 grains in one pint." Only six of 166 patients passed over 300 ounces in one day. The highest sp. gravity recorded is 1054, although repeatedly it was found above 1045. The highest percentage of sugar mentioned was 12.5 per cent. In many instances there was present between 9 and 10 per cent of sugar.

The finding of sugar in the urine was determined in

the first instance until 1851 by means of the taste. The physician in charge sometimes called upon the house physician to apply this test, although a positive statement to this effect is found only in 1844 and again in 1845. It is probable, however, that the patient was occasionally called upon to use this method, for in 1831 the statement appears, "on tasting, as directed to do by the physician . . . it was found sweet." This patient is credited also with the ability to make quantitative determinations in this way, for "he observed, however, that if he relapsed at any time, even in a very slight degree from a rigid animal diet, the urine was increased correspondingly in sweetness and quantity." In another instance it is stated that the urine is "less sweet after eggs." In general the patient at the time of entrance was able to make such positive statements as made apparent the condition of the urine. One "reports urine sometimes natural, at others sweet." It had the "sweetest taste," or was "sweetest to the taste." The urine had a "saccharine smell and taste," or presented a "sugary appearance on the shirt," or the "urine upon cloth leaves sticky and sparkling deposit." The intelligence of the lower animals sometimes aided in the diagnosis, for of one patient's urine it is stated that "flies gathered upon places moistened by it." Such everyday methods of diagnosis are still in use, for it is but recently that an office patient stated of her diabetic mother that her "clothes would rattle like starch, so sugary was the water, like brine on the floor."

These rude methods of testing the saccharine condition of the urine were supplemented in 1827 by evaporating the specimen. It is recorded "urine yesterday sixteen ounces, . . . seven ounces this morning, . . . sixteen being boiled about two remains (*sic*), resembling molasses, of saccharine smell and taste." In the following year, "urine seven pints, natural appearance, without sediment, not giving syrup on evaporation." It is stated also that eight ounces of urine yielded one ounce of syrup, and at the end of the record of the autopsy of a fatal case it appears that specimens of the saccharin matter and of the nitrate of urea prepared from the urine on different days by Dr. Chas. T. Jackson will be found in the cabinet of the Soc. for Medical Improvement, Nos. 566 and 567.

In 1833 we learn that "one quart of urine boiled to the consistency of thick molasses weighed two and one-half ounces. On the 12th the same quantity boiled as before weighed three ounces." This method was still in vogue in 1842 for "two ounces carefully evaporated gave about a drachm of clear extract of the color and consistency of treacle," and four years later the evaporating method still was employed.

In 1841 Trommer's test was made known (*Annal. der Chemie und Pharmacie*, 1841, xxxix, 360) and in 1842 the hospital records state that the "urine was unaffected by heat, nitric acid or aqua potassa." In this year the fermentation test also was first employed.

Although Moore's test had been made known in 1844, the first mention of its use in the hospital was in 1851, when the following record appears: "glucose strongly marked on the addition of heat and liquor potassæ."

In 1852 Dr. Bacon determined, by what means it is not stated, that the per cent of sugar in a given urine was 4 per cent and two years later the fermentation method was employed for ascertaining the percentage.

The breath of diabetic patients first attracted attention in 1835, when a man entered the hospital with a note from his physician stating that it had a "peculiar sour smell." The observation made of this patient while in the hospital was of "a curious smell in breath which he has had since entrance." In three cases the breath is stated to have the odor of new milk. In 1846 it is noted of one of these "odor of breath considered by some of aromatic sweetness." Other expressions are in 1846 "odor of boiled milk;" in 1848 "ward distinctly tainted with smell peculiar to diabetes," "fruity odor;" in 1869 "sweet chloroform-like smell in neighborhood of patient's bed."

That the acetone odor of the breath then was attracting general attention is apparent in 1847 from the statement made in Watson's *Practice* (op. cit. p. 868) that "according to Dr. Prout the scent somewhat resembles that of sweet hay, but to my nose it is more like the smell of certain apples or rather of an apple chamber." He attributes the peculiar odor to the sugar. In 1866 in *Harley on Diabetes* (op. cit.) there is no mention of acetone or of diacetic acid, although Petters (*Prager Vierteljahrsch.* 1857, lv) several years before had attributed the coma of diabetes to the former agent.

Acetone was sought for in the breath of 19 cases, and in the urine of 24 cases. Its presence was indicated by the odor in 16 of the former, and by chemical tests in 14 of the latter series. It is interesting to note in connection with the result of recent investigations on the increase of acetone in consequence of a change to an absolute proteid diet, that the records state in 1894 that the "acetone smell has been more since disappearance of sugar than at any other time." Ten days later, however, without any change in diet there had been

no return of sugar and no smell to the breath.

The ferric chlorid reaction, which, when positive, is considered generally to be evidence of the presence of diacetic acid, was sought for in 22 cases and found in 13. Albuminuria was present in the urine in 67 cases and was absent in 60 cases. Casts were found in 36 cases.

In four instances only is there a record of the examination of the feces. In 1844 a patient reported that his "food frequently passes away in lumps undigested" and fat is reported as absent in the stools of three patients.

In six cases there was tinnitus aurium and two patients had sciatica. Sexual power is noted as absent in 9 cases and present in 4. The catamenia were present in 11 cases and absent in 9. Jaundice is mentioned to have occurred in five cases, and three of these patients died in the hospital, one of pneumonia and one of atrophied pancreas. Syphilis is stated to have existed in one case. Diabetes and myxedema coexisted in one patient and in another diabetic there was a tumor of the thyroid body. Three of the patients suffered from gangrene of the toe, a fourth had a gangrenous slough of the tissues of the leg, and a fifth died with a carbuncular-like inflammation of the thigh. Three of the patients had abscesses, one being of the hip, another of the wrist, both cases ending fatally. The third abscess was of the jaw, but the patient grew better. In one case there was a round ulcer of the toe, which improved under treatment.

The records afford some evidence concerning the duration of the disease, which in one case is stated to have existed for twelve years, while three patients had suffered but two weeks. Of the latter, one died, one was relieved and one unrelieved. The average duration was one year and a half.

The length of the illness in the fatal cases is indicated in the following table:

DURATION	NUMBER OF CASES
From 0 to 1 year	27
From 1 to 2 years	7
From 2 to 3 years	3
From 3 to 4 years	1
From 4 to 5 years	0
From 5 to 6 years	1
From 6 to 7 years	1
Unknown	7
	47

These cases, necessarily those of grave diabetes, thus ended fatally in nearly three-fourths of the number in which this point could be determined within one year after the disease made itself manifest, and within two years in nearly seven-eighths of the entire series. That diabetes may prove fatal at the end of a longer period of time, from 6 to 7 years as in one instance, is attributable to the well-known fact that cases of mild diabetes may become suddenly severe, and that the symptoms of this disease may for a while disappear to return at a later period. An illustration of the latter condition, one which may be called recurrent diabetes, is to be found in the record of a patient who was in the hospital in 1862. In March, 1861, he suffered from cough with abundant yellow expectoration. In the latter part of the month the thirst increased and became excessive; the patient drank freely and passed large quantities of pale urine. The appetite failed and there was progressive debility. At the end of four months the quantity of urine became normal. The patient remained apparently well until the following February, when excessive thirst, polyuria and debility returned, and it was observed that the urine left a sticky and sparkling deposit on cloth. Another instance of recurrence is noted in 1866. Two years previous to the entrance of this patient he observed that an abnormally large quantity of urine was being passed in the twenty-four hours and that the thirst was excessive. These and other symptoms continued for three months and then disappeared without treatment. At the end of eighteen months, however, they returned, accompanied by general weakness and faintness. It is recorded that the house physician tasted the urine of the patient.

Of the 172 patients 47 or 27 per cent died. The mortality among the 127 male patients was 39 or 30.7 per cent; of the 45 female patients 8 died, a mortality of 17.7 per cent. The death rate among the males thus proved nearly twice as high as among the females. The following table illustrates the variation in the rate of mortality during successive periods of years.

Period	No. of cases	No. of deaths	Percentage of deaths
From 1824 to 1840	7	1	14
From 1840 to 1855	16	7	44
From 1855 to 1870	24	5	20
From 1870 to 1885	39	11	28
From 1885 to 1898	86	23	27
From 1824 to 1898	172	47	27

It has previously been remarked that from 1824 to 1885 there were treated 86 cases, the same number of cases as in the period from 1885 to 1898. It is certainly noteworthy that in each of these intervals there

was an average of 27 per cent of fatal cases, which again was the average mortality rate of the cases treated throughout the entire period from 1824 to 1898. It might be thought from the inspection of this table that the method of treatment was superior from 1824 to 1840 and from 1855 to 1870 and that in the intervening years it was inferior. The information on this point later given affords no justification for such an inference.

Although it appears from the study of the records that most cases of grave diabetes die within a year or two of the onset of the disease and that 27 per cent of all cases are fatal, some evidence has been obtained with regard to the prognosis in the individual case. Heredity appears to have less importance than is usually assigned to it. Of ten cases in which heredity may have been of etiologic significance three died, while of thirty-two cases in which heredity had no influence eight died. Thus the percentage of deaths was merely a trifle higher in those cases in which an inherited tendency to diabetes may have played a part than in those in which no such influence existed.

The time of life at which the patient suffers from the disease appears to be of greater prognostic importance, as may be inferred from the following table:

Age	No. of Cases	Deaths	Per cent
From 0 to 10 years	3	1	33
From 10 to 20 years	15	3	20
From 20 to 30 years	41	14	34
From 30 to 40 years	43	13	30
From 40 to 50 years	29	4	14
From 59 to 60 years	28	5	18
From 60 to 70 years	11	5	45
	170	45	

Thus about one-third of the patients suffering from diabetes during the first ten years of life and between the ages of 20 and 40 years die, and nearly one-half of the cases between 60 and 70 years prove fatal. The number of cases of diabetes in young children, however, is so small as not to be of much value in generalizing. The high rate of mortality after the age of 60 is due, possibly, only indirectly to the diabetes, the patients perhaps being unable to resist the effects of other disease, even if mild, in the presence of so grave an affection.

Thirty-eight of the 47 fatal cases died comatose, the coma lasting one day in 10 cases, two days in 14 and three days in 5 patients. In the remaining 9 cases the duration of the coma was not to be determined. The frequency of the coma in relation to the age of the patient is indicated in the following table:

Age	No. of cases	Deaths from coma	Per cent
From 0 to 10 years	3	1	33
From 10 to 20 years	15	3	20
From 20 to 30 years	41	12	29
From 30 to 40 years	43	9	21
From 40 to 50 years	29	3	10
From 50 to 60 years	28	4	14
From 60 to 70 years	11	3	27

The suddenness of its onset in certain instances is apparent from the record of a patient in 1828 who was able to leave the hospital for a few hours, at the end of which he became comatose and died. In 1846 another patient absented himself from the hospital without leave and became intoxicated; two days later he was comatose and died at the end of another two days. On the other hand, a third patient while in the hospital became intoxicated, had no coma and lived.

It is to be observed that of twenty fatal cases of diabetes there was present chronic nephritis in six, pulmonary tuberculosis and carbuncle or gangrene each in three, myocarditis in two and pneumonia, pleurisy, cerebral thrombosis, alveolar abscess and atrophied pancreas each in one. A patient with diabetes suffered at the same time from acute catarrhal cholangitis, acute rheumatism and chronic bronchitis.

The study of the records of these cases affords some evidence relating to the prognostic value of the presence of acetone and diacetic acid. Although the odor of acetone was present in the breath of 12 out of 14 fatal cases, that is, in more than 85 per cent, and in the urine of 6 out of 9 fatal cases, namely 66 per cent, in which the records show that attention was directed to this point, it was present also in the breath of 4 out of 5 nonfatal cases, 80 per cent, and in the urine of 8 out of 15 nonfatal cases, 53 per cent. It is evident from this comparison that the presence of an acetone odor in the breath or in the urine throws but little light upon the severity or mildness of the disease.

The ferric chlorid reaction was present in 6 out of 8 fatal cases and in one-half of the 14 nonfatal cases in which it was sought for. This evidence, so far as it goes, therefore, is in support of the view that this reaction has a somewhat serious significance.

It is interesting to note that in the earliest days of the hospital the improvement of the patient's condition was based upon an increase in weight.

It is to be remembered that John Rollo ("Notes of a Diabetic Case," 1897) first ascertained that an animal diet not only decreased the quantity of urine, but also diminished the amount of sugar. The diet, therefore,

from 1824 to 1840 was based evidently upon this discovery and the first diabetic patient in the hospital was fed on "animal food and bread in small quantities. Only one potato (*sic*) at dinner." Later molasses, beer and apples were excluded from his diet. In 1827 a patient's fare consisted of two eggs, at a meal, meat, milk, butter and salt. Such a diet, however, was not exclusive, for mention is made that vegetable food and sugar were not to be taken, but rice and milk porridge were allowed. Toast, water and broth were permitted, and crackers were given instead of bread. Thirst was quenched with chamomile tea or balm tea, and lemons also served for this purpose.

The unlimited use of liquids was not permitted, for one patient was allowed only a "teacup of liquid at meals." Another was given, "balm tea as little as will suffice," and it is stated of a third that he "thinks he has not drank all his allowance."

The first treatment the first patient received was a warm bath, and as the quantity of urine appeared to be less after the bath had been taken it was ordered to be repeated every other day. Warm salt baths also were used.

The advantages of exercise were appreciated at an early period, for one patient in 1831 was advised to ride horseback, and another was recommended to take as much exercise as his strength would permit.

Alcohol was given as early as 1828, when the physician in charge ordered, "let her take some brandy and water, taking one teaspoonful of brandy in hot or cold water, repeating it once in 3 or 4 hours if the effects are grateful." There is nothing in the record to show that its action was displeasing to the patient. The recent investigations of von Noorden ("Die Zuckerkrankheit und Ihre Behandlung," 1895, 146), show that this treatment has a sound scientific basis since one gram of alcohol is the equivalent of seven calories, while the same quantity of proteids and carbohydrates is equivalent only to four calories.

This patient was treated also with opium and "by error took following in A. M.

℞ Infus. Sennæ Comp., ℥iij."

On the next day he "was uncomfortable in head with some depression of spirits." During this patient's stay in the hospital he was ordered powdered rhubarb and the infusion of rhubarb and magnesia; a trial was made also of uva ursi and of the sodium and potassium tartrate.

During the first fifteen years the treatment in general consisted of opium, either alone or with camphor and aloes. Cathartics were used liberally, and frequent mention is made of rhubarb, aloes, colocynth, senna, calomel, magnesium sulphate, castor oil and croton oil. Enemata were employed freely, some of them being especially designated "active." One patient who complained of nausea promptly received a dose of ipecac.

Among other drugs in use during this period were quinin and dilute nitric acid, the decoction of sumac and powdered guiac.

Blisters and cupping often were used, and one patient "thinks opium and blisters have been followed by the greatest improvement." More severe counter-irritation was ordered sometimes, as appears from the record, "apply caustic issue on each side of the spine." In one case this application proved to be directly injurious.

During the period of high mortality, that is from 1840 to 1855, the following dietary is ordered: "Lean meat, with a small quantity of stale, dry or toasted bread, avoiding all fatty, farinaceous and saccharine articles. For drink, cold water and weak tea." The use of liquids continued to be restricted, although slippery elm tea now came into use. Alcohol was not given regularly, and blisters no longer were applied. Leeches appeared to serve in the place of the latter and of issues for it is recorded, "Leach (*sic*) bites now ulcerated."

Opium continued to be given, but not so largely as previous to 1840. Cathartics were prescribed with freedom, and the liberal use of calomel is suggested by the frequent records of spongy gums and myrrh mouth washes. Iron now was used in the form of the tincture of the chlorid or the carbonate. Other remedies employed were argentic nitrate, ammonium hydrosulphuret, ammonium carbonate, conium, hyoscyamus and valerian, aromatic sulphuric acid and creosote. During this period the use of yeast was tried by McGregor (*Watson's Practice,* p. 872), who stated that it made the patients feel as if they were "on the eve of being blown up." A patient in the hospital was ordered to "take yeast ℥ss. in milk *ter die.*" This quantity was increased to an ounce daily and then was resumed and omitted at intervals during a month, the yeast being taken five-sixths of the time. The effect was not that mentioned by Watson, but a sense of constant nausea was the chief resulting complaint.

From 1855 to 1870 especial attention was paid to the selection of a suitable bread, and bran bread, stale bread, brown dyspepsia bread, toasted dyspepsia bread, ship biscuit and toasted ship bread were ordered. Butter, cabbage, cheese and greens were allowed, but shellfish and liver were excluded. Liquids at times were restricted, and

cocoa was given somewhat frequently. Alcohol was ordered occasionally, and one patient, notwithstanding milk punch was prescribed *p.r.n.*, remained in the hospital but a single day, at the end of which he was discharged unrelieved. Opium was but little used, counter-irritants were discontinued and there was but little variety in the use of drugs. One patient received a half pint of iron rust water at dinner. To another in 1866 was given a half ounce of cod liver oil three times daily. As "she likes it and don't have enough," the dose was increased to three ounces three times daily. This maximum dose was reduced in consequence of the production of loose movements of the bowels.

From 1870 to 1885 gluten bread was used, but was discovered to contain 33 per cent of starch. Patients were advised "to drink as little water as possible," but as much as four quarts of skim-milk were given daily. Opium and codeia were used frequently, but alcohol, blisters, baths and exercise were not advised as a part of the routine treatment. On the contrary, a large number of drugs were employed, including Fowler's solution, bromid of arsenic, antimony, bismuth, phosphate of zinc, phosphorus, bromid of potassium, iodid of potassium, sulphid of calcium, salicylate of sodium, hydrochloric acid, lactic acid, gallic acid, pilocarpin, chloral, ergot, pepsin, Wilbur's oil and Shaw's pill. One patient received what was called the glycerin treatment, instituted by Schultzen (Naunyn, "Der Diabetes Mellitus," 1898, 405). On the day after his admission he was given thirty-three ounces of glycerin and died comatose on the same day. The coma was accompanied by spasms, to relieve which ether was given, but the house physician apparently feared that the death might be attributed to the effects of the ether.

In the period since 1885, Soya bean bread has been added to the dietary, and fats are used with freedom. The use of water is frequently, by no means always, restricted, and the use of skim-milk gradually has lessened. Alcohol, baths and exercise, are not made matters of routine. Opium and codeia are more often used than before, and trials have been made with potassium citrate, lithium carbonate, jambul, salol, salicin, antipyrin and urethan. Saccharin occasionally is used. Up to this period comatose patients had been treated solely with stimulants and diuretics, and brandy, nitroglycerin and oxygen were given frequently at the onset of coma. The use of solutions of sodium chlorid or sodium bicarbonate in enema, subcutaneous injection or by transfusion was begun and eight patients were thus treated. Although these patients died, as had those otherwise treated, it appears from the records that in certain instances life was somewhat prolonged. The patient's mind usually became clearer after the administration of the saline, and one person was aroused to such a degree that he is recorded to have said, "Oh! doctor, I'm glad you did that; I have not felt so well for a long time."

The practical outcome of this examination of the records of cases of diabetes treated at the Massachusetts General Hospital during the past seventy-four years can be stated in a very few words. The average mortality of saccharin diabetes has not changed materially, for it was the same in the past thirteen years as in the previous sixty-one years. The dietetic restrictions have undergone no essential alteration in this time. Opium is the only drug which has been persistently used in the treatment throughout this entire period.

ORGANIZATION SECTION

ELECT NEW OFFICERS FOR 1955-56

At the Business Session of the Fifteenth Annual Meeting of the American Diabetes Association, held in Atlantic City, New Jersey, June 4-5, Henry T. Ricketts, M.D., Chicago, was elected President for this organizational year, to succeed Henry B. Mulholland, M.D., Charlottesville. Frederick W. Williams, M.D., New York, was elected First Vice President; John A. Reed, M.D., Washington, D.C., Second Vice President; and Franklin B. Peck, Sr., M.D., Indianapolis, Secretary. William H. Olmsted, M.D., St. Louis, was re-elected Treasurer. Drs. Ricketts and Williams served in 1954-55 as First and Second Vice Presidents, respectively. These officers will serve until the Sixteenth Annual Meeting of the Association, which will be held in Chicago June 9-10, 1956.

At this meeting, Robert H. Williams, M.D., Seattle, and John E. Howard, M.D., Baltimore, were elected to the Council for the three-year term ending in 1958. Charles H. Best, M.D., Toronto, Canada, was elected to fill the unexpired term, ending in 1957, of Franklin B. Peck, Sr., M.D.

A complete summary of the meeting, including reports of the Nominating Committee and of Officers and other Committees, will be published in the forthcoming issue of DIABETES.

AWARD TWO RESEARCH FELLOWSHIPS

The Committee on Research and Fellowships announces the award of Fellowships to E. Rudolf Froesch, M.D., Peter Bent Brigham Hospital, Boston, and to John A. Owen, Jr., M.D., Duke University, Durham, N.C. Dr. Froesch is to work with Albert E. Renold, M.D., on the determination of glucose by glucose oxidase and its clinical applications. Dr. Owen will work with Frank L. Engel, M.D., on the diabetogenic action of pituitary growth hormone in rats.

Plans are being made to award at least one Fellowship for the academic year 1956-57. Requests for application forms and other inquiries should be addressed to the Association's Executive Director, Mr. J. Richard Connelly, who will forward the information to the Committee on Research and Fellowships.

SORBITOL RESEARCH GRANT

The sum of $7,500 is available to individuals for research on the metabolism of sorbitol in the human diabetic, funds for that purpose having been accepted by the Council of the American Diabetes Association from the Atlas Powder Company. The outline of research, including personnel and physical facilities, should be submitted to the Chairman of the Committee on Research and Fellowships of the American Diabetes Association at the National Office.

ADA MEMBERS TO ATTEND SECOND IDF CONGRESS

Many members of the American Diabetes Association have made plans to attend the Second Congress of the International Diabetes Federation to be held in Cambridge, England, July 4-8, 1955. As previously announced, Henry T. Ricketts, M.D., newly elected President of the American Diabetes Association, has been named official Medical Delegate to the Congress. Mr. J. Richard Connelly, Executive Director, is Lay Delegate.

SIXTEENTH ANNUAL MEETING IN CHICAGO, JUNE 9-10, 1956

The Drake hotel will serve as headquarters for next year's Annual Meeting of the American Diabetes Association, to be held June 9-10, prior to the Annual Session of the American Medical Association, June 11-15. An announcement of the Sixteenth Annual Meeting was mailed to ADA members under date of May 11, 1955, which included an inquiry as to planned attendance. Answering the inquiry does not commit any member to attend, but will assist in making hotel arrangements to accommodate members during the Association's meeting as well as during the AMA session.

DALLAS SITE OF FOURTH POSTGRADUATE COURSE

The American Diabetes Association will conduct the Fourth Postgraduate Course in Diabetes and Basic Metabolic Problems at the Statler Hotel in Dallas, Texas, Jan. 25-27, 1956. It will be followed by the midyear meeting of the Council of the ADA on Jan. 28-29.

The invitation to hold the Course was extended, on behalf of the Dallas Diabetes Association, by Edwin L. Rippy, M.D., a Councilor of the American Diabetes Association, and Chairman of the Committee on Policies. This will be the first time in the 15-year history of the Association that a meeting has been held in the southwestern part of the United States.

The faculty of the Course will consist of outstanding physicians from Dallas and other cities of that area,

members of the American Diabetes Association's Council, and other distinguished physicians. Those who plan to attend are urged to register as soon as possible. All inquiries and applications should be addressed to the National Office. A public meeting, co-sponsored with the Dallas Diabetes Association, will also be held in conjunction with the Course. Many members of the faculty will participate in this program.

LOWER SUBSCRIPTION RATES FOR MEDICAL STUDENTS, INTERNS, RESIDENTS

The special price of $4.50 a year, half of the regular subscription rate, is now offered to Medical Students, Interns and Residents. This reduction was recommended by the Committee on Scientific Publications, and accepted by the Council.

SCIENTIFIC EXHIBITS AVAILABLE

The American Diabetes Association has three scientific exhibits available for display at meetings of the Affiliate Associations and other medical organizations. These exhibits are entitled "The Management of Diabetes Mellitus," "Vascular Complications of Diabetes," and "Diabetes Detection by the Physician." They can be obtained without cost, since shipping charges both ways will be assumed by the Association. The Council has appropriated funds for this activity to the end of the current fiscal year, April 30, 1956.

NEW MEMBERS

The following Active Members were elected as of May 1 and June 1, 1955:

California
Hudson, Charles B. — Oakland
Nielsen, Robert F. — Redondo Beach
Connecticut
Marshall, James S. — Farmington
District of Columbia
Magee, Joseph H. — Washington
Illinois
O'Neill, James B. — Chicago
Iowa
Englund, Philip M. — Fort Dodge
Massachusetts
Nichols, Nancy — Brookline
Roehrig, Charles B. — Brookline
Tatlock, Hugh — Northampton
Whitehouse, Fred W. — Brookline
Michigan
Aiuto, James J. — Grosse Point
Minnesota
Grosh, John L. — Rochester
McSweeny, Austin J. — Rochester
New Jersey
Joelson, Robert H. — Paterson
New York
Halfaer, Bertram — Niagara Falls
North Carolina
Tuttle, James G. — Albemarle
Ohio
Ames, Charlotte L. — Xenia
Oklahoma
Austin, Frank H. — Lawton
Oregon
Page, Otto C. — Portland
Schneider, Harold O. — Salem
Pennsylvania
DiGeorge, Angelo M. — Philadelphia
Dineen, Francis A. — Pittsburgh
Hahn, Karl W. — Bethlehem
Wisconsin
Conway, James P. — Milwaukee

Other Countries

Canada
Rabinovitch, Sam — Montreal
Italy
Signorelli, Saverio — Catania

The following Associate Member was transferred to Active Membership as of May 1, 1955:
Kentucky
Sullivan, Clarence F. — Louisville

NEWS NOTES

FIRST HOSPITAL TEACHING CLINIC FOR DIABETICS

Contracts have been let for the construction of the world's first Hospital Teaching Clinic for diabetics, it was announced recently by Elliott P. Joslin, M.D., of Boston, Mass. This modern, two-story, million-dollar clinic building, to be constructed as part of the New England Deaconess Hospital, will occupy the lot on the corner of Joslin and Pilgrim roads, opposite Harris Hall and the Deaconess Building.

The clinic will carry on and expand the work of the Joslin group and the Deaconess Hospital in the prevention of the disabling conditions of late diabetes.

The building will have two stories and a basement. The latter will contain records, bookkeeping files, secretarial forces, secretaries' and residents' rest rooms, laboratory, sterilizing, X-ray and supply room.

A part of the basement and most of the first floor will be rented by the Joslin Clinic. The second floor will be devoted entirely to patients and arranged in one-, two-, and four-bedrooms, with toilets and complete facilities including nurses' station, utility room, kitchen, dining room, baths. Diagnostic offices will be arranged on both sides of the two interior corridors. There is a sub-basement under the West end with a tunnel connection to the Deaconess Hospital.

SEVENTH POSTGRADUATE ASSEMBLY IN ENDOCRINOLOGY AND METABOLISM

The Seventh Postgraduate Assembly in Endocrinology and Metabolism, sponsored jointly by The Endocrine Society and the Indiana University School of Medicine, will be held at the Indiana University Medical Center, Indianapolis, Ind., Sept. 26-Oct. 1, 1955.

The faculty will consist of twenty-one eminent clinicians and investigators in the fields of endocrinology and metabolism. The program will cover the various endocrinopathies, with emphasis on the clinical aspects, demonstration of laboratory tests, presentations of cases, and question-and-answer panel discussions.

The course has been designed to cover the main aspects of diagnosis and therapy in the fields of endocrinology and metabolism for the physician in general practice and for those in other specialities who wish to have a general knowledge of this rapidly growing field.

For further information concerning the program, write Postgraduate Office, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7, Ind. Registration is limited to 100; tuition fee is $100. Arrangement for housing will be made through the University.

FIRST WOODYATT MEMORIAL LECTURE

The first in a series of annual lectures in memory of Roland Turner Woodyatt, M.D., internationally known Chicago physician, medical teacher and investigator, was given May 20 under the auspices of Northwestern University Medical School. Evarts A. Graham, Emeritus Professor of Surgery at Washington University, St. Louis, Missouri, and a close friend of Dr. Woodyatt, delivered the initial memorial lecture. Dr. Woodyatt, who died in 1953, devoted his professional life to the study of diabetes and was well known for his achievements in the care of diabetic patients.

Dr. Woodyatt served for six years as a member of the Council of the American Diabetes Association at the time of the founding of the organization. He was the Banting Memorial Lecturer at the Annual Meeting of the Association in Chicago in 1948.

Personals

NORMAN H. JOLLIFFE, M.D., presided over the first day's session of the two-day conference on "Nutrition in Infections," held at the Barbizon-Plaza Hotel, New York, under the auspices of the New York Academy of Sciences on Tuesday and Wednesday, May 24 and 25, 1955. Dr. Jolliffe is Director of the Bureau of Nutrition, Department of Health, New York City.

LAURANCE KINSELL, M.D., Highland Alameda County Hospital, Oakland, California, spoke on "Nutritional and Metabolic Aspects of Infection" at the Wednesday morning session.

HERBERT POLLACK, M.D., College of Physicians and Surgeons, Columbia University, New York, talked on "Altered Prognosis in the Diabetic with Infection" at the Wednesday afternoon session.

R. D. LAWRENCE, M.D., London, England, presented The Lilly Lecture at the Thirty-sixth Annual Session of the American College of Physicians, in Philadelphia, Pa., on April 28, 1955. The title of the lecture was "Three Types of Human Diabetes." Dr. Lawrence, an Honorary Member of the American Diabetes Association, is Physician-in-Charge, Diabetic Department, King's College Hospital, London, England.

Obituary

HAROLD VOGT GOULD, M.D., was born in 1889 in Buffalo, New York, and died in Chicago on Feb. 22, 1955. He graduated from the University of Illinois College of Medicine in 1912, interned at Ravenswood Hospital, 1912-13, and was certified by the American Board of Internal Medicine in 1937. In addition to membership in the American Diabetes Association, which he joined in 1942, Dr. Gould was a member of the American Heart Association, Chicago Medical Society (Trustee 1937-46), Secretary of North Shore Branch 1922-23, and President of North Shore Branch 1923-24. On the Attending Staff at Ravenswood Hospital since 1918, Dr. Gould was Staff Secretary 1919-25, Staff Vice-President 1926-27, and Staff President the following year; he was first permanent Chairman of the Medical Section.